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ORIGINAL ARTICLES

SOME QUANTITATIVE OBSERVATIONS ON A METHAMPHETAMINE-PHENOBARBITAL ANOREXIC COMPOUND IN OBESE OUTPATIENTS

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Many practicing physicians feel that weight reduction is merely a matter of will power on the part of the patient and that the physician and adjuvant drugs are essentially of psychologic importance.

An opposing school of thought supports the thesis that anorexic compounds are necessary for sustained adherence to a basically difficult and unpleasant regimen of dietary restriction. For many physicians, the office treatment of the obese patient is a frustrating and disheartening experience. A major reason for this is that most physicians have no clear idea of the expected quantitative responses of their obese patients on weight reduction programs. If their doctors are uncertain, the patients are even more so.

Data collected in the present study provide information on two practical problems: 1) the relative roles of will power and anorexic drugs in promoting continued adherence to restricted diets, and 2) the role of the physician's personality in encouraging patients to "stick to" their weight reduction programs. In addition, this study provides an interesting comparison of double-blind and single-blind techniques in the clinical evaluation of an anorexic drug.

Methods and Procedure. The patients reported in this study were registered in a special obesity clinic in the outpatient department of a large hospital. All of the patients were under the care of the co-authors of this paper. They were subjected to the same weight reduction program with respect to diet, frequency of visits to the clinic, and method by which the drugs were administered. The only major variables consisted of the drug dispensed (the real drug or the placebo) and the supervising physi-

cian either B.S. or L.W.). A uniform, 1000-calorie, high-protein diet was prescribed for each patient. The diet contained 100 gm. of carbohydrate, 84 gm. of protein, and 30 gm. of fat. In addition, all patients were given a therapeutic vitamin capsule to be taken just before lunch and two other tablets to take "for reducing."

The active medication was furnished in two sizes: one an enteric-coated controlled-release extended action tablet (Ambar Extentabs) containing the active agents, methamphetamine hydrochloride, 10 mg. and phenobarbital, 64.8 mg. This tablet was taken immediately before breakfast. A smaller tablet containing 3.33 mg. of methamphetamine hydrochloride and 21.6 mg. of phenobarbital (Ambar) was taken at 5 p.m. Identical placebos were prescribed for the patients who served as controls.

Each patient was seen weekly for 4 weeks and then once every 2 weeks for a maximum of 20 weeks. Each patient continued on either the real medication or the placebo from the beginning to the end of the study.

Although reported in a single paper, the study was conducted in two parts which ran concurrently. One was a double-blind study in which 30 patients were started on active drug and 23 on placebo. Alternate, unselected patients were assigned first to one physician and then to the other. Alternate patients assigned to each doctor were then given the real medication and the placebo in turn. Thus, each of the physicians supervised a *real medication group* and a *placebo group*. In the single-blind study, 27 patients were started on Ambar and 21 on placebo, according to the same process of assignment.

The mean age of the patients in the double-blind study was 50 to 53 years and in the single-blind from 43 to 48 years. In the double-blind study, the patients were an average of 55% to 62% overweight and in the single-blind study, 36% to 43%. Thus, these patients were obviously obese middle-aged individuals, mostly women.

The degree of weight loss was expressed as the average pounds lost per patient, the average pounds lost per patient per week, and the average performance index per patient. The performance index (P.I.) of a patient, according to the formula of Jolliffe and Alpert[4], is the $\frac{\text{actual weight loss}}{\text{predicted weight loss}} \times 100$. A perfect performance index is 100% and values less than 100% indicate the approximate degree of the patient's adherence to the dietary program. Use of the performance index eliminates several possible variables by permitting comparison between individuals of different sexes, ages, occupations, activities, weights, and degrees of obesity.

Results. The number of patients observed at different periods of time up to 20 weeks are shown in the following table.

TABLE 1.—NUMBER OF PATIENTS PERSISTING IN TREATMENT

Type of Study	*Medication*	*(4-Week Periods)*				
		1	*2*	*3*	*4*	*5*
Double-blind	Ambar	27	21	17	14	10
	Placebo	22	20	15	9	7
Single-blind	Ambar	26	23	15	10	4
	Placebo	19	18	11	7	3

It appears from these figures, therefore, that patients taking the active drug were not "held" in the study any better than patients taking the placebo. There are so many unrelated factors which influence the holding power of weight reduction programs that this problem could be a suitable subject for a separate study.

The average pounds lost per patient per week by 4-week intervals are listed in Table 2. The same information is presented in Table 3 using the performance index as the measure rather than actual pounds lost.

From these tables it can be seen that the greater loss of weight by the *real medication group* was statistically significant by both means of computation in both the double-blind and single-blind study. Moreover, the order of magnitude of the various indexes of weight loss was approximately the same for both the double-blind and single-blind studies.

WEIGHT LOSS AT 4-WEEK INTERVALS. Although total weight loss is of interest to the reader who views the study as an accomplished fact, the week to week

loss over a period of months is of utmost importance to the patient and the physician, for it is this tangible evidence of success that encourages the patient to continue. Tables 2 and 3 show that the greatest rate of weight loss for both groups occurs in the first 4-week period. In the next 3 periods (two, three, and four) the mean rate of weight loss for the *real medication group* is continuous and steady at a

DOUBLE-BLIND STUDIES. Although weight losses are remarkably similar for both the *real medication* and *placebo groups* in both the single-blind and double-blind studies, there are two minor differences: (1) In the single-blind study, some of the differences between the *real medication group* and the *placebo group* were more obvious than in the double-blind study. (2) The double-blind study showed greater difference

TABLE 2.—WEIGHT LOSS PER PATIENT PER WEEK BY 4-WEEK PERIOD

Type of Study	*Medication*	*Average Pounds Lost per Patient per Week*				
		Period 1	*Period 2*	*Period 3*	*Period 4*	*Period 5*
Double-blind	Ambar	1.8 ± 0.2°	1.2 ± 0.2	0.9 ± 0.1	1.0 ± 0.2	0.7 ± 0.1
	Placebo	1.3 ± 0.2	0.2 ± 0.2	0.1 ± 0.1	0.3 ± 0.2	0.2 ± 0.2
Single-blind	Ambar	1.9 ± 0.1	1.4 ± 0.1	1.1 ± 0.2	0.5 ± 0.2	0.6
	Placebo	0.9 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	−0.1 ± 0.5	0

°Mean and Standard Error of the Mean.

TABLE 3.—AVERAGE PERFORMANCE INDEX BY 4-WEEK PERIOD

Type of Study	*Medication*	*Average Performance Index (expressed as %)*				
		Period 1	*Period 2*	*Period 3*	*Period 4*	*Period 5*
Double-blind	Ambar	62 ± 6.0	41 ± 5.9	35 ± 4.1	38 ± 5.8	26 ± 4.2
	Placebo	40 ± 5.7	7 ± 5.9	3 ± 5.1	10 ± 6.5	10 ± 7.9
Single-blind	Ambar	72 ± 5.6	52 ± 3.7	42 ± 5.8	19 ± 6.3	19
	Placebo	30 ± 7.2	11 ± 6.9	11 ± 6.4	2 ± 13.5	1

mean loss of one pound per week, or a P.I. of 40%. On the other hand, the weight loss of the *placebo group* dips sharply in the second period and remains very low in all succeeding periods. For example, the mean rate of weight loss for the *placebo group* in periods 2 to 5 is 0.2 pound per week, or a P.I. of 7.5%. Thus, the major effect of medication on weight loss may be seen in the 5th to 16th week of dieting.

COMPARISON OF SINGLE-BLIND AND

between the *real medication group* and *placebo groups* in the fourth and fifth periods, probably because of the smaller numbers of patients in these last two periods in the single-blind study.

When the weight loss data and the performance index of the patients were tabulated separately according to the supervising physician, there was no difference statistically between the weight loss of the patients supervised by B.S. and those of L.W. (see Table 4). In this connection, it must be re-

membered that both physicians worked under exactly the same methodology.

Discussion. The total weight loss of patients given a methamphetamine-phenobarbital compound (*real medication group*) was significantly greater than the loss achieved by patients in the *placebo group*. This was true in both the double-blind and single-blind study. The average weight loss of 1.2 pounds per week over a 15½-week period, achieved by the patients in the *real medication group*, compares very favorably with rates of loss recorded in the literature for other anorexic agents. Studies on the efficacy of various amphetamine drugs (Gadek *et al.*[2], Gelvin and McGavack[3], Osserman and Dolger[5], Roberts[6], Williams *et al.*[7]) have generally indicated average weight losses varying from 1 to 2 pounds per week over varying periods of time.

Of special importance is the observation that the rate of weight loss is not constant with the passage of time. In the first 4 weeks of the double-blind study, the placebo patients lost weight almost as well as did the patients on the real medication. However, in succeeding weeks, the weight loss in the *placebo* patients dropped off to 0.2 pound per week, compared to a steady loss of 1.0 pound per week by the *real medication* patients. These observations would imply that a psychogenic impetus influences weight loss for about 4 weeks, after which it has no favorable influence on the results. It would seem equally clear that a proposed therapy or therapeutic agent must prove its effectiveness for more than 4 weeks if more than psychologic or placebo merit is to be ascribed to it. Further, it is obvious that the results are influenced by the length of time that the patients are under observation; the rate of loss is higher with short-term therapy and lower with longer-term therapy.

TABLE 4.—RESULTS OF WEIGHT REDUCTION THERAPY, BY PHYSICIAN. REAL MEDICATION. PERFORMANCE INDEX AT 4-WEEK INTERVALS

Type of Study	*Physician*	*4-week Periods* 1	2	3	4	5
Double-blind	B.S.	63% (15)*	40% (13)	35% (10)	36% (8)	26% (7)
	L.W.	60 (12)	41 (8)	36 (7)	41 (6)	26 (3)
Single-blind	B.S.	75 (18)	53 (15)	44 (10)	15 (6)	19 (3)
	L.W.	65 (8)	49 (8)	37 (5)	26 (4)	20 (1)

*Number of Patients.

The absence of any significant difference in results achieved by the double-blind as opposed to the single-blind method of study suggests that double-blind techniques are not really necessary for the evaluation of therapeutic agents whose effectiveness can be measured by objective means (the weight of the patient in this particular study). Double-blind techniques are quite necessary on the other hand, when the endpoint is subjective (as for example, pain).

The close correlation of results achieved by each of the physicians in

this study implies that the use of a standard methodology to approach the problem of weight reduction may reduce the influence of the physician's personality on the results achieved. In this connection, it is well to recall Eberlein's[1] assertion that one of the most important factors in successful weight reduction is the physician's interest in the problem. In this study, both physicians were greatly interested in the patient's desire to lose weight. The similarity of their results indicates that their psychological influence was approximately equal and that the significant difference between the *real medication* and *placebo group* was due to the anorexic agent.

Summary. The value of a methamphetamine-phenobarbital anorexic agent (Ambar) was evaluated in 101 patients by the single-blind and double-blind method. The over-all loss of weight achieved by patients taking the active medication was significantly greater in both the double-blind and single-blind groups than that achieved by patients on placebo medication. The greatest effect of drug therapy was observed from the 5th to 16th week of therapy, after psychogenic influences had largely ceased to influence the degree of weight loss.

The close similarity of results in the double-blind and single-blind studies suggest that single-blind methods are as suitable as double-blind when an objective indicator such as weight loss is used to evaluate effectiveness. The absence of a discernible difference in the influence of the physician's personality on the results under constant methodological conditions further strengthens the validity of the observed drug effect.

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SUMMARIO IN INTERLINGUA

Observationes Quantitative Super le Effecto de Un Composito Anorexic a Methamphetamino-Phenobarbital in Obese Patientes Visitante

Le valor de un agente anorexic a methamphetamino-phenobarbital (Ambar) esseva evalutate in 101 patientes per le methodos uni- e bilateralmente occulte. Le perdita total de peso obtenite per le patientes qui recipeva le medication active esseva significativemente plus grande in le gruppo "unilateralmente occulte" e le gruppo "bilateralmente occulte" que in le gruppo de patientes recipiente

le placebo. Le plus marcate effecto del droga esseva observate durante le intervallo ab le quinte usque al dece-septe septimana del therapia, quando le influentias psychogenic habeva cessate plus o minus completemente afficer le grado del perdita de peso.

Le intime similitude del resultatos in le studios bilateralmente occulte e unilateralmente occulte suggere que methodos del secunde de iste duo typos es tanto fidel como methodos del prime typo quando indicatores objective, tal como le perdita de peso, es usate pro evalutar le efficacia de un droga. Le absentia de un discernibile differentia in le influentia del personalitate del medico super le resultatos, quando le conditiones methodologic es constante, corrobora additionalmente le validitate del observate effectos de droga.

SUMMARIO IN INTERLINGUA

(See page 539 for original article)

Nivellos Seral de Propionato de Erythromycina e le Effectos Clinic Obtenite per Ille Droga

In studios cruciate, le concentrationes seral de erythromycina e oleandomycina e de lor esteres esseva determinate post unic administrationes al hasardo de doses de 250 mg. In plus, le maximos del concentrationes seral de erythromycina e de propionato de erythromycina esseva mesurate post quatro doses administrate a intervallos de 8 horas. Specimens de sanguine esseva obtenite 2 e 4 horas post le administration del quarte dose. Le methodo a placa e anulo, con le uso de *Sarcina lutea*, esseva empleate como standard de essayage antibiotic. In plus, le activitate de erythromycina, de oleandomycina, e de lor plus active esteres esseva mesurate contra *Staphylococcus 209P*, con le uso de turbidimetria a varie nivellos de pH.

Post doses unic e comparate con respecto al activitate erythromycinic, propionato de erythromycina monstrava le plus alte nivello seral medie. In le studio a dosage multiple in que erythromycina e propionato de erythromycina esseva comparate, le nivellos seral esseva plure vices plus alte in le caso del estere propionylic. Le activitate antistaphylococcic, tanto in le caso de propionato de erythromycina como etiam in le caso de triacetyloleandomycina, esseva marcatemente reducite in tanto que le medios deveniva plus acidic.

Cinquanta patientes con infectiones respiratori e de tissu molle causate per un varietate de organismos Gram-positive esseva tractate con propionato de erythromycina. Le responsas esseva favorabile in omne le casos, excepte 5. Duo occurrentias de serie effectos lateral esseva incontrate. Le un esseva un caso de enterocolitis staphylococcic. In le altere caso il se tractava de retardate hypersensibilitate con prurito e eosinophilia. In ambe casos, abstention ab le droga esseva necessari.

SERUM LEVELS AND CLINICAL RESULTS WITH ERYTHROMYCIN PROPIONATE*

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Erythromycin is one of the most useful therapeutic agents for infections caused by Gram-positive cocci. The outstanding virtues of this antibiotic are its clinical effectiveness, low toxicity and infrequent side-effects. Erythromycin has been a common replacement for penicillin, particularly in patients who have had allergic reactions. The purpose of the present study was to observe the blood levels, clinical effectiveness and side-effects of erythromycin propionate in man.

Because erythromycin is rapidly absorbed into the blood when taken by mouth, this route of administration is preferred for all patients who are able to swallow and retain the antibiotic. Parenteral preparations are available for the remaining cases. Inasmuch as erythromycin base is inactivated by gastric juice, oral preparations have usually been made in the form of coated tablets which resist acid digestion yet dissolve in alkaline intestinal juices; in some cases this enteric coating interferes with the absorption of the drug from the intestine. Unfortunately the level of activity in the serum of many normal adults after a single dose of two coated tablets containing 500 mg. of erythromycin is too low to measure (Albright and Hall[1]).

Recently Stephens and Conine[10] reported that the propionate monoester of erythromycin, bonded at the hydroxyl group on the desosamine ring, has properties which appear to make it the best available oral preparation of erythromycin. Comparison with erythromycin showed that the propionate yielded superior average blood levels after a single dose. Experiments by Lee *et al.*[6] established that the ester had the same low toxicity for laboratory animals that is characteristic of erythromycin. The propionyl ester was found to be slowly excreted in the bile, thus accounting for the higher blood levels. Griffith and his group[2] found that in man 80% of the urinary erythromycin is in the form of the ester. In dogs and rats the ester is hydrolyzed.

Griffith and his coworkers[2] also found that a single dose of erythromycin propionate produced much higher blood levels than those found with the base. In a preliminary clinical study,

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good results were noted in 19 patients. Most of these had soft tissue infections caused by hemolytic streptococci or staphylococci. The only side-effects observed were minimal gastrointestinal symptoms.

Hirsch, Kunin and Finland[5] compared the post-ingestion serum level obtained with erythromycin propionate with that of triacetyloleandomycin. With the more potent propionate, serum antibacterial activity measured in broth dilutions against pathogenic *Staphylococcus 209P* and *Streptococcus 98* was much higher. The superiority of this erythromycin ester over the oleandomycin ester was confirmed by the cup-plate method, when the serum activity was expressed in terms of a single antibiotic standard.

The largest published series of patients having infections treated with erythromycin propionate is the 105 cases reported by Smith and Soderstrom[9]. The daily dose was 1.0 to 2.0 gm. by mouth. Improvement was noted in soft tissue infections, osteomyelitis, pharyngitis, and pneumonia. Side-effects were minimal. Six patients had some gastric distress and 2 cases had loose stools. One patient had a fatal hematemesis, the cause of which was unknown.

Methods. Serum levels of antibiotic activity were measured with five preparations of erythromycin as well as with triacetyloleandomycin in 10 healthy adult males of the laboratory staff. All the antibiotics were given in gelatin capsules, except erythromycin stearate. The latter was given in the form of a carbowax-coated tablet as well as in a capsule. They were given 2 hours after breakfast immediately after withdrawal of 12 ml. samples of venous blood. Each subject was given one dose equivalent to 250 mg. of antibiotic base with water. Further blood samples were obtained at 2 and 4 hours. The serum was then separated, frozen and stored. At the conclusion of the experiment each subject had ingested six antibiotic preparations in random order.

The standard cup-plate method of Grove and Randall[3] was used for assay of the antibiotic activity of the serum, employing *Sarcina lutea* as the test organism. All serums were compared for antibiotic activity with standard solutions of erythromycin and oleandomycin. The standard activity curves were obtained from averages of a duplicate series of determinations. In each case the values for diluted standard antibiotic solutions fell close upon a straight line. Assays of undiluted serums were carried out in triplicate and the average value of the activity calculated. For each of the six antibiotic preparations the average level of serum activity (at 2 hours and 4 hours) and the standard deviation from the mean were calculated. The statistical significance of the differences between the means of the peak concentrations was calculated.

Another two-way crossover experiment was performed to compare peak serum levels of erythromycin base and the propionate after multiple oral doses. The base was given as an enteric-coated tablet and the propionate in a gelatin capsule to 8 subjects. The two antibiotics were administered in random order one week apart. After a control blood sample was drawn, 500 mg. of either antibiotic was ingested every 8 hours for 4 doses. Blood specimens were obtained 2 and 4 hours after the fourth dose, and the serum was separated and frozen preparatory to antibiotic assay.

The activity of the antibiotic bases and their esters was tested at various levels of pH by the tube dilution method (Waisbren, Carr and Dunnette[12]). The medium employed was BHI broth (Difco) with .025 M. lactic acid, adjusted with N. HCl or NaOH to the desired pH. The antibiotics were dissolved in methyl alcohol and diluted with phosphate buffer pH 8.0 (Grove and Randall[3]). One milliliter of a 10^{-4} dilution of a fully grown broth culture of *Staphylococcus 209P* was added to the antibiotic broths (2 ml.). After incubation at 35° C. for 24 hours, the growth was measured turbidimetrically and compared to an antibiotic-free control.

CLINICAL STUDIES. Fifty patients with a Gram-positive coccal infection were selected for therapy with propionyl erythromycin (Ilosone). In all but 3 patients, bacteriological data were obtained. The pertinent findings are summarized in Table 4.

Two-thirds of the patients were males over 40 years of age; only 3 females were included in the study. The majority of patients presented an acute illness, but 17 had recently received one or more antibiotics. Of these, 4

had mixed infections and the remainder had either inadequate therapy or superinfection.

Oral therapy was instituted in dosages varying from 0.25 to 0.5 gm. every 6 hours. The larger dose was recommended for staphylococcal infections. Short courses of chemotherapy were advised: either 7 or 10 days. The minimum therapeutic dose was 6.0 gm.; the maximum was 197 gm. The latter patient received 4.0 gm. daily for 45 days. The average total dose was 16.7 gm. in 48 cases; excluding 2 chronic infections.

Results. SERUM LEVELS. The average levels of serum activity for six antibiotic preparations are shown in Table 1. Preparations A and B were given as "unknown" capsules designated only by code numbers until the assays were completed. With antibiotics D and E, it was necessary to omit the values for one subject because control serum samples had some activity. All values in the table are expressed in terms of erythromycin base activity. It may be seen that "peak" concentrations, 2 to 4 hours after a single dose of 250 mg., showed considerable differences. Erythromycin propionate gave the highest levels in serum (preparations A and C). Triacetyloleandomycin (E) produced somewhat lower levels in terms of erythromycin activity, although the concentration of oleandomycin was high. Erythromycin stearate in coated tablets (D) gave lower but satisfactory levels. Erythromycin stearate (B) and erythromycin base (F) in unprotected capsules showed rather low serum activity. The statistically significant differences in peak serum activity are given in Table 1. It is noteworthy that with all preparations considerable variation existed in peak levels of serum activity; however, no individual could be characterized as having markedly high or low values for all six antibiotic forms.

TABLE 1.—ERYTHROMYCIN ACTIVITY EQUIVALENT IN BLOOD AFTER INGESTION OF 250 MG. OF VARIOUS ANTIBIOTIC PREPARATIONS

Antibiotic and Source	*Form*	*No. of Subjects*	*Av. Serum Level in μg./ml.* 2 hr.	4 hr.
A. Erythromycin propionate (Abbott)	Capsule —125 mg.	10	.53 ± .48	.40 ± .29
B. Erythromycin propionate (Abbott)	Capsule —125 mg.	10	.09 ± .08	.07 ± .04
C. Erythromycin propionate Ilosone (Lilly)	Capsule —250 mg.	10	.48 ± .43	.55 ± .13
D. Erythromycin stearate Erythrocin (Abbott)	"Filmtab" —250 mg.	9	.19 ± .19	.31 ± .28
E. Triacetyloleandomycin Cyclamycin (Wyeth)	Capsule —250 mg.	9	.37 ± .18*	.29 ± .12*
F. Erythromycin (Lilly)	Capsule —250 mg.	10	.04 ± .02	.06 ± .02

Significant Differences in Peak Concentrations	A-B	A-F	B-C	B-D	B-E	C-F	D-F	E-F
P value	.005	.0024	.0004	.0203	.0001	.0001	.0058	<.0001

*Oleandomycin activity equivalent = .91 ± .70 μg. per ml. at 2 hr. and .51 ± .24 at 4 hr.

In Table 2 are given the average peak levels of serum erythromycin activity after the fourth 500 mg. dose of the base (G) and the propionate (H). Two subjects given erythromycin were omitted from the study because they failed to take the 4 doses. The average

serum level of erythromycin activity was significantly higher at all times for the propionate than for the base. Variation was noted between the subjects assayed; however, in all but 2 cases the serum levels were higher with erythromycin propionate.

Erythromycin propionate and triacetyloleandomycin, as well as their antibiotic bases, were shown to have less activity against *Staphylococcus 209P* when the pH of the medium was reduced from 7.4 to 5.9. As shown in Table 3, the minimal antibiotic concentration required to inhibit bacterial growth was increased three-fold or more when the pH was reduced about one unit.

TABLE 2.—PEAK BLOOD LEVEL AFTER INGESTION OF FOURTH 500 MG. DOSE OF ERYTHROMYCIN OR ERYTHROMYCIN PROPIONATE GIVEN EVERY 8 HOURS

Antibiotic	*Form*	*No. of Subjects*	Av. *Serum Level in μg./ml.*° 2 hr.	4 hr.
G. Erythromycin Ilotycin (Lilly)	Enteric coated tablet	6	1.18 ± .80	.95 ± .37
H. Erythromycin propionate Ilosone (Lilly)	Capsule	8	2.24 ± 1.03	2.51 ± .64

°Significance of differences		P value
G-H	2 hr.	.0357
G-H	4 hr.	<.00001
G-H	Peak - Peak	.001

TABLE 3.—ACTIVITY OF ERYTHROMYCIN, OLEANDOMYCIN AND SOME ESTERS AT VARIOUS LEVELS OF pH

Antibiotic	*Minimal Inhibitory Concentration° in μg./ml. at pH's* 7.4	6.7	6.5	6.4	6.0	5.9
Erythromycin	<.10	.15	.3	.3	.4	.4
Oleandomycin	.15	>.45	.6	>.45	>.45	>.45
Erythromycin propionate	>.05		.3		1.3	
Triacetyloleandomycin	.6		1.5			

°Tube dilution method in BHI broth with .025M. lactic acid. Test organism = *Staphylococcus 209P.*

CLINICAL STUDIES. Defervescence occurred within 48 hours in 24 patients; noted in 45 patients; of the remaining, 4 were considered therapeutic failures (Table 4).

Pneumonia. There were 26 patients representing various types of pneumonia (Table 5). Objective response was generally rapid, within 24 to 48 hours. With the exception of one patient, resolution was complete. The single therapeutic failure in this category was case 15 with bronchogenic

carcinoma and pneumonia. Two patients severely ill with pneumonia are presented:

TABLE 4.—CLINICAL FEATURES IN 50 CASES GIVEN ERYTHROMYCIN PROPIONATE

Age:	
19 – 39	14
40 – 60	16
>60	20
Sex:	
Male	47
Female	3
Duration of Symptoms:	
<24 hours	7
24 – 72 hours	17
4 – 7 days	12
> 1 week	14
Temperature (at Adm.):	
<100° F.	18
100 – 101.9°	18
102 – 103.9°	9
>104°	5
Leukocytes:	
<10,000	14
10 – 15,000	18
15 – 20,000	8
>20,000	7
(not done	3)
Complications:	
Atelectasis	3
Pleural Effusion	1
Staphylococcal enterocolitis	1
Side-Effects:	
Diarrhea	3
Pruritus with eosinophilia	1
Nausea	1
Clinical Response:	
Improved	45*
Failure	4
Therapy too brief to evaluate	1

*Includes 2 cases in which combined therapy was required.

Case Reports. CASE 24. R.D., a 23-year-old man with diabetes mellitus of 10 years' duration controlled with a diabetic diet and 60 units of NPH insulin, was admitted with ketosis and bronchopneumonia. On admission, the blood glucose was 510 mg. per 100 ml.; the serum bicarbonate was 8.3 mEq. per L.; the leukocytes numbered 21,550 per c.mm. with a shift to the left. Vigorous fluid replacement corrected the electrolyte imbalance. Ilosone, 250 mg. every 6 hours, was given orally. Within 48 hours he was afebrile. Chest roentgenogram revealed complete resolution after 14 days.

CASE 40. L.C., a 60-year-old white man with chronic lymphatic leukemia and staphylococcal bronchopneumonia, had received chloramphenicol together with steroids and chlorambucil, without any change in the clinical picture. The addition of Ilosone, 500 mg. every 6 hours for 10 days, brought about resolution of the pneumonia and return of the white blood cell count to normal.

At the time of admission, 4 of the 26 patients with pneumonia were found to have pleural effusion or empyema. Of this group, 2 had fluid localized in a major fissure; these responded to chemotherapy alone. One localized effusion, secondary to streptococcal lobar pneumonia, responded slowly to Ilosone, 250 mg. every 6 hours for 36 days, together with thoracentesis. Residual atelectasis and pleuritis were noted. Only one patient with frank empyema (*Diplococccus pneumoniae,*) was encountered. This patient received the unusually high dose

TABLE 5.—TYPE OF INFECTIONS TREATED AND ORGANISM RECOVERED

CASES TREATED:		
Pneumonia		26
Lobar	6	
Bronchopneumonia	20	
Soft tissue and skin infections		13
Pharyngitis or tonsillitis		5
Miscellaneous infections		6
Total		50
ORGANISM RECOVERED:		
Strep. viridans		9
Beta hemolytic streptococcus		9
Staph. aureus		9
D. pneumoniae		6
H. influenzae		1
Proteus vulgaris		1
Pseudomonas aeruginosa		1
Mixed flora		11
No culture		3
Total		50

of 4.0 gm. daily for 45 days, together with rib resection and surgical drainage. No untoward side-effects occurred and recovery was uneventful.

Skin and Soft Tissue Infections. Four postoperative wound infections were treated. Response was rapid, as was noted in case 38 with a *Beta* hemolytic streptococcal wound infection. Prior therapy with procaine penicillin had failed to alter the clinical picture. Ilosone, 250 mg. every 6 hours for 10 days, caused the suppuration to cease with the subsequent development of healthy granulation tissue. Two patients with furunculosis responded immediately and did not require surgical drainage. One patient with a carbuncle required incision and drainage. One second-degree burn with associated lymphangitis was treated for 10 days with gradual decrease in swelling. Another infected third-degree burn (hemolytic *Staphylococcus aureus* and a *Beta* hemolytic streptococcus) responded to Ilosone and was successfully grafted. One case of *Meleny's ulcer,* which had failed to respond to a multitude of antibiotics, responded nicely to combined chemotherapy with erythromycin propionate, penicillin and streptomycin. In addition, one case of erysipelas was seen. Therapy with Ilosone, 400 mg. every 6 hours, resulted in a marked decrease in periorbital edema within 48 hours. One case of pyoderma and a case of cellulitis responded to Ilosone.

Pharyngitis and Tonsillitis. Three cases of *Beta* hemolytic streptococcal pharyngitis and 2 cases of tonsillitis were treated with an average dose of 10.8 gm. of erythromycin propionate. Recovery was complete in all.

Miscellaneous Infections. Of the remainder, 3 cases of acute exacerbations of chronic bronchitis were successfully treated. One case of streptococcal parotitis was treated with Ilosone, 500 mg. every 6 hours, together with incision and drainage; recovery was complete within one week. One case of staphylococcal enterocolitis responded to short-term Ilosone therapy. This group also includes a therapeutic failure with aplastic anemia and pseudomonas bacteremia (Case 6).

Combined therapy was undertaken in 10 cases. Two cases (6 and 15) represent therapeutic failures. In 2 of the remaining 8 cases, Ilosone was added to the antibiotic regimen with rapid improvement (Cases 2 and 32). Case 39 (tuberculosis) received only 3 oral doses of Ilosone when therapy was discontinued because rapid lysis failed to occur. Seven cases with combined therapy are summarized below:

Case Reports. CASE 2. A chronic unresolved streptococcal bronchopneumonia was previously treated with procaine penicillin-G and chloramphenicol without clearing. Ilosone 500 mg. four times daily for 5 days brought about prompt Roentgen resolution.

CASE 6. Aplastic anemia with pancytopenia, initially treated with Ilosone for a staphylococcal ulcer, succumbed to a pseudomonas bacteremia despite steroids, neomycin and penicillin.

CASE 15. Bronchogenic carcinoma with obstructive pneumonitis failed to respond to either Ilosone, 2.0 gm. daily for 10 days, or chloramphenicol. Radiotherapy did offer relief.

CASE 16. A Meleny's ulcer, initially treated with Ilosone, 500 mg. every 6 hours, and procaine penicillin-G with improvement; addition of streptomycin accelerated healing.

CASE 32. Pyoderma, due to *Staphylococcus aureus,* failed to respond to penicillin and streptomycin. Replacement with Ilosone, 500 mg. every 6 hours, brought rapid resolution within 4 days.

CASE 33. Aspiration pneumonia, due to *H. influenzae,* ran a remittent febrile course which failed to respond to Ilosone, 250 mg. every 6 hours. Addition of chloramphenicol brought about resolution.

CASE 39. Patient with delirium tremens with bronchopneumonia received only 3 doses of Ilosone before it was replaced with penicillin and streptomycin. This patient was later noted to have active pulmonary tuberculosis.

Four of 26 patients treated for acute bacterial pneumonia had concurrent active tuberculosis; for completeness, they are included in this group of combined therapy.

COMPLICATIONS. Of the 26 patients with pneumonia, 3 had residual atelectasis and one developed a sterile pleural effusion 2 weeks after the onset of chemotherapy. The single case of aspiration pneumonia had evidence of chronic bronchitis, by bronchogram, 2 months after combined chemotherapy with chloramphenicol and Ilosone.

A major complication of staphylococcal enterocolitis and pancreatitis occurred in one patient 11 days after chemotherapy was begun. His case is summarized below:

CASE 17. A 33-year-old engineer with streptococcal pneumonia was treated for 11 days with Ilosone, 2.0 gm. daily in divided doses. Clinical and radiographic responses were rapid. On the eleventh hospital day he complained of mild epigastric distress and passed two loose stools. The temperature rose to 102° and his condition worsened, with the development of a paralytic ileus and hyperpyrexia of 106° (orally). Stool cultures yielded hemolytic staphylococci, coagulase-negative, which were resistant to the broad spectrum antibiotics and erythromycin. Vital signs remained stable. Treatment consisted of ice-packing, nasogastric suction, and two 4.0-gm. doses of neomycin. Four days later the urinary amylase, previously normal, rose to 1,031 units per hour; thereafter recovery was uneventful.

Side Effects. Of the 50 patients treated, signs of toxicity (including enterocolitis) occurred in 6. Of these, 3 had diarrhea and one complained of nausea, which was relieved when the drug was taken with milk. Case 4, pneumococcal bronchopneumonia with pleural effusion, was treated for 32 days with Ilosone, 1.0 gm. daily, with gradual resolution. On the thirty-fourth day, he complained of generalized pruritus, and the blood eosinophil count, previously normal, rose to 19%. This patient had mild hepatic cirrhosis with a reversed albumin-globulin ratio and a slight bromsulfalein retention of 7.5%. Discontinuance of therapy brought prompt subsidence of symptoms.

Discussion. The subject of serum levels of erythromycin, oleandomycin and their derivatives has been recently reviewed by Hirsch and Finland[4]. A single oral dose of triacetyloleandomycin, given after breakfast, will give a higher serum antibiotic *concentration* than erythromycin propionate. Erythromycin has greater antibacterial activity than does oleandomycin. Erythromycin propionate will produce higher levels of antibacterial *activity* when compared to a single antibiotic standard, whether it be erythromycin or oleandomycin (Hirsch, Kunin and Finland[5]).

The present single-dose crossover study has confirmed this observation (Table 1). As shown by Hirsch and Finland[4], the blood levels for propionyl erythromycin and erythromycin stearate might have been higher if our subjects had been fasted. Food seems to reduce gastrointestinal absorption of erythromycin and its esters but not that of triacetyloleandomycin (Hirsch and Finland[4]).

The formulation of various preparations of the erythromycin group of antibiotics has been extensively explored by the pharmaceutical industry. Erythromycin propionate and triacetyloleandomycin are virtually tasteless in comparison with their bases and salts. These antibiotic esters have been found to lose much less of their activity upon contact with gastric juice than is the case with their bases and salts. Erythromycin stearate is inactivated to a considerable extent by gastric juice. Erythromycin propionate and triacetyloleandomycin need not be dispensed in tablets with enteric coatings. Although the latter may protect the unstable antibiotic bases from gastric in-

activation, they delay intestinal absorption. The fact that these antibiotic esters and their bases have less activity against bacteria in acid media than at pH 7.4 (Table 3) may be of significance in infected suppurative lesions. In a crossover study by Reisch and his coworkers[8], blood levels after multiple doses of erythromycin were compared with triacetyloleandomycin. Average serum levels, 2 hours after a fourth 500 mg. dose, were not significantly different. It has been demonstrated in the present study (Table 2) that under similar conditions erythromycin propionate, however, does give significantly higher blood levels than erythromycin.

Erythromycin propionate appears to be effective in the treatment of Gram-positive infections. In the 3 clinical series thus far reported (Griffith *et al.*[2], Perry, Hall and Kirby[7], Smith and Soderstrom[9]), good results were obtained in the therapy of pneumococcal, streptococcal and staphylococcal infections. Our present study confirms those findings. In general, the side-effects attributable to this drug have been minor; nausea and diarrhea have seldom occurred. The incidence of serious side-effects to erythromycin has also been minimal. Welch *et al.*[13], in reporting 74 cases of enterocolitis following antibiotic therapy, attribute only one case to erythromycin. In preliminary animal toxicity studies with erythromycin propionate, Lee and his group[6] reported no significant pathological changes in dogs.

In our present series one case of staphylococcal enterocolitis and pancreatitis was encountered. The drug was administered in a daily dose of 2.0 gm. for 11 days; diarrhea and fever occurred on the eleventh day. It is possible that superinfection might have been due to the drug. In general, 1.0 gm. daily for 7 to 10 days appears to be adequate for the usual infection encountered.

Another patient, with pruritus and eosinophilia, was thought to have had a delayed hypersensitivity reaction. Stryker, Siegel and Grolnick[11], reporting on the allergenicity of erythromycin, state that "the incidence is so small as to be considered insignificant." Inasmuch as less erythromycin is excreted in the bile in cases receiving erythromycin propionate, the possibility that this reaction could be related to hepatic dysfunction deserves further investigation. In the presence of preexisting liver disease, long-term chemotherapy with large doses of erythromycin propionate may be unwise.

Summary and Conclusions. 1. Crossover studies, determining the concentrations of erythromycin, oleandomycin and their esters after single, random 250-mg. doses were carried out; in addition, peak serum concentrations of erythromycin and erythromycin propionate were measured after four 8-hour doses. Blood samples were obtained 2 and 4 hours after the fourth dose. The cup-plate method, employing *Sarcina lutea*, was used as the standard antibiotic assay. Furthermore, the activity of erythromycin, oleandomycin, and their most active esters were measured against *Staphylococcus 209P*, employing turbidimetric technique at various pH levels.

After a single dose, when compared on the basis of erythromycin activity, erythromycin propionate showed the highest average serum level. In the multiple dose study, comparing erythromycin and erythromycin propionate, serum levels were several times higher for the propionyl ester. The antistaphylococcal activity, for both erythromycin propionate and triacetyloleandomycin, was markedly reduced as the media became more acidic.

2. Fifty patients with respiratory and

soft tissue infections due to a variety of Gram-positive organisms were treated with erythromycin propionate. Response was favorable in all but 5 cases. Two serious side-effects were encountered, one case of staphylococcal enterocolitis and one case of delayed hypersensitivity with pruritus and eosinophilia. Both necessitated withdrawal of the drug.

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(Interlingua on page 538)

USE OF SULFADIMETHOXINE IN THE PREVENTION OF STREPTOCOCCAL INFECTIONS IN RHEUMATIC PATIENTS

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The introduction for clinical use of sulfonamides which are characterized by slow excretion and prolonged maintenance of significant concentrations of free drug in the serum began with sulfamethoxypyridazine in 1957 (Roepke, Maren and Mayer[6]). A second compound of this family has recently been developed, sulfadimethoxine (4-sulfanilamido-2,6 dimethoxypyrimidine).

Its administration is followed by high serum concentrations for 24 hours and moderate concentrations for 72 hours (Boger[2], Sawchuk[7]). The usual sulfonamide antibacterial spectrum has been noted to be present and toxicity studies in animals indicated a good therapeutic range (Sawchuk[7]). For the foregoing reasons, sulfadimethoxine may have special convenience in situations requiring prolonged therapy with sulfonamides. For example, the use of sulfonamides for the prophylaxis of group A beta hemolytic streptococcal infections in patients who have had rheumatic fever is widely known; but the difficulties encountered with this type of prophylaxis, in the form of patient cooperation, are also noteworthy (Am. Heart Assn.[1]). Since less frequent administration is required to achieve prolonged blood concentrations of sulfadimethoxine, this study was undertaken to ascertain its potential as a prophylactic drug in rheumatic fever patients when given at weekly intervals. Lepper, Simon and Marienfeld[5] and Johnson, Mathews and Stollerman[4], have similarly investigated the effect of sulfamethoxypyridazine as a prophylactic agent in convalescent patients with rheumatic fever with good results. A comparison of the former study with this one is possible since the circumstances under which the data were obtained were similar.

Methods. Twenty-eight of the patients at Herrick House, the convalescent home for patients with rheumatic fever in Bartlett, Illinois, were treated with sulfadimethoxine* from July 20, 1958, to November 23, 1958. The remaining patients at Herrick House were treated with penicillin or sulfadiazine. Some were on no prophylactic medication. Sulfadimethoxine was given in a dose of 30 mg. per kg. once weekly, and serum for sulfonamide concentrations were obtained just prior to the next weekly dose. The serum was stored in the frozen state and all determinations were made after the study was completed. Only the free sulfonamide concentration was measured by the Bratton-Marshall method[3].

*Generously provided by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

The 28 patients were observed over a period of 257 patient weeks, and the 54 patients, constituting the control group, were observed over a period of 179 patient weeks. Weekly throat cultures were obtained for group A beta hemolytic streptococci as in the previous study (Lepper, Simon and Marienfeld[5]). Twenty-five patients had three or more weekly observations.

serum levels of sulfadimethoxine in this study ($t = 0.36$). Only 7 of the 25 patients had all determinations above 1 mg. per 100 ml. Among the other 18, the frequency of concentrations below this level ranged from 16.6 to 100%. The only characteristic of the group

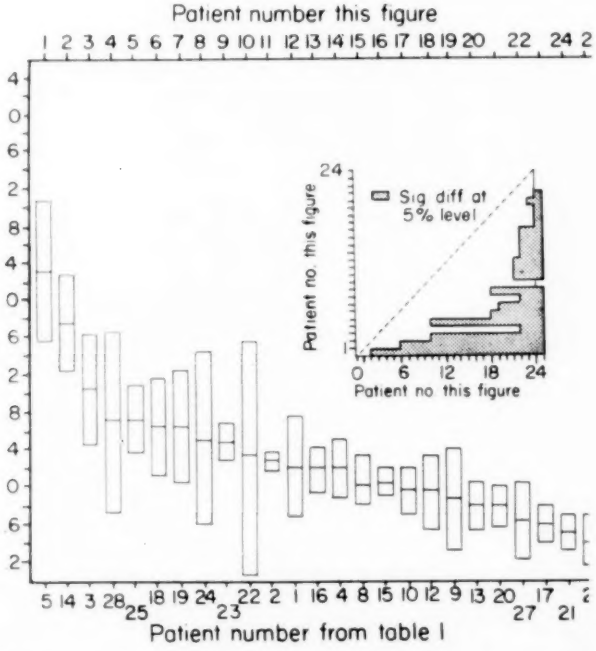

Fig. 1.—Means of repeated determination of serum sulfadimethoxine concentrations one week after the administration of a weekly dose of 30 mg./kg. The range represents + or — two standard errors. The insert indicates by the solid bar the patients represented on the ordinate in whom the mean of the determinations were significantly different from the means of the patients represented on the abscissa.

Results. SERUM CONCENTRATIONS. Table 1 and Fig. 1 give the means and standard deviation of concentrations of sulfadimethoxine in the serums of the 25 patients who had three or more weekly determinations. Six patients, who received sulfadiazine taken from Lepper's study, are compared. There was no significant difference between the mean levels of sulfadiazine and the lowest with serum levels below 1 mg. per 100 ml. which separated the groups was an average age of 8.9 years, whereas the average age of the children with concentrations over 1 mg. per 100 ml. was 12.3 years. The average weight of the former group was 60 lbs. (range 48 to 85) while in the latter group, it was 92 lbs. (range 50.5 to 144). Among the entire 114 serum concentrations in-

cluded in Table 1, 45 were of the low order of magnitude of less than 1 mg. per 100 ml.

On the other hand, as shown in Fig. 1, the mean value for the free sulfonamide concentration among the 25 patients with three or more determinations were frequently significantly with sulfadimethoxine, throughout the 257 patient weeks, there was one positive throat culture for group A beta hemolytic streptococci. Among the 54 untreated patients who were observed a total of 179 weeks, there were four positive throat cultures for group A beta hemolytic streptococci. The one

TABLE 1.—FREE SULFONAMIDE SERUM CONCENTRATIONS ONE WEEK AFTER ADMINISTRATION OF 30 MG./KG. OF SULFADIMETHOXINE

Patient	*Wkly. Determ.*	*Sulfonamide Conc. mg./100 ml.* Mean ± 2 SD.		*Weekly Determ. Below 1 mg./100 ml.* No.	% of Total
I	6	1.2	0.67	3	50
II	4	1.3	0.1	0	0
III	6	2.0	0.71	0	0
IV	4	1.2	0.32	1	25
V	7	3.3	0.99	0	0
VIII	6	1.0	0.26	1	16.6
IX	7	0.9	0.67	5	71
X	5	0.9	0.28	3	60
XII	5	0.9	04.7	3	60
XIII	7	0.79	0.35	5	71
XIV	4	2.8	0.52	0	0
XV	5	1.0	0.17	2	40
XVI	5	1.2	0.26	1	20
XVII	3	0.6	0.17	3	100
XVIII	4	1.6	0.52	1	25
XIX	4	1.6	0.59	0	0
XX	4	0.8	0.22	3	75
XXI	4	0.5	0.17	4	100
XXII	3	1.3	1.1	2	66 2/3
XXIII	4	1.5	0.2	0	0
XXIV	4	1.5	1.2	1	25
XXV	3	1.7	1.05	0	0
XXVI	3	0.4	0.22	3	100
XXVII	4	0.7	0.48	3	75
XXVIII	3	1.7	0.83	1	33 1/3
Total	114	1.3	0.48	45	39.5
Sulfadiazine°	6	0.65	0.43		

°Data from paper of Lepper, Simon and Marienfeld[5].

different. This illustrates that there was some consistency of the serum concentration in the same patient at the low point. Moreover, in some patients this therapy would appear much more adequate than in others.

BACTERIOLOGICAL RESULTS. Among the group of 28 patients under treatment failure in prophylaxis occurred simultaneously with an outbreak of acute follicular tonsillitis in members of the personnel, the onset of which was noted on October 26, 1958. Among the staff, positive throat cultures were noted sporadically from October 26 through November 23, 1958. As seen

in Table 2 during this time there were 104 weeks of observation of the personnel with 7 positive cultures, 40 weeks with 4 positives in the untreated patients and only 1 positive culture in 74 weeks among the patients who were treated with sulfadimethoxine.

Institution of therapy was prompt in patients with positive cultures and no recurrences of rheumatic fever occurred in either group. Antistreptolysin titers

nausea and vomiting with generalized erythema of the skin. In this patient the symptoms subsided within 24 hours after the drug was stopped. Occasional complaints of headache were noted, but the drug had to be discontinued only in the 2 patients described.

Discussion. The desirability of the simplicity of a drug which could be given at weekly intervals by mouth successfully to prevent the infection by

TABLE 2.—OCCURRENCE OF POSITIVE THROAT CULTURES FOR GROUP A BETA HEMOLYTIC STREPTOCOCCI IMMEDIATELY BEFORE AND AFTER THE FIRST POSITIVE WAS OBTAINED

	Personnel of House		*Untreated Patients*		*Patients Treated with Sulfadimethoxine*	
Date of Cultures	*No. Cult'd.*	*No. Positive*	*No. Cult'd.*	*No. Positive*	*No. Cult'd.*	*No. Positive*
Oct. 5, 1958	24	0	4	0	14	0
Oct. 13, 1958	24	0	4	0	14	0
Oct. 26, 1958*	18	2	6	1	15	0
Nov. 2, 1958	18	4	5	0	15	1
Nov. 9, 1958	20	0	6	2	16	0
Nov. 16, 1958	24	0	11	1	14	0
Nov. 23, 1958	24	1	12	0	14	0

*Date on which first evidence of outbreak was obtained.

were falling at the time the throat cultures were positive, and they continued to decrease. The serum level of sulfadimethoxine was substantially lower in the patient who developed the positive throat culture than the mean for the entire group of the children. However, there were patients with serum levels below 0.5 mg. per 100 ml. who did not have positive throat cultures.

TOXIC REACTIONS. Toxic reactions occurred in 2 patients. One developed moderately severe angioneurotic edema associated with mild fever and discomfort. Blood pressure, urinalysis and blood counts remained normal. The edema persisted for 6 days after the medication was stopped. Another patient developed fever of 103° F.,

streptococci of children who have had rheumatic fever has been pointed out (Lepper, Simon and Marienfeld[5]). From the previous study with sulfamethoxypyridazine this goal seemed to be within reach in most patients, but the reliability of the plasma concentration obtained indicated a narrow margin of protection. When sulfadimethoxine became available it was felt that an investigation similar to that previously performed with the earlier analogue would indicate whether the new agent would be potentially more useful.

In Table 3 it is evident that with each of the agents there is a rather wide range of the minimal blood concentrations just before the next dose.

However, the levels were constant enough in the individual patients, though there were significant differences between the means of multiple determinations on the same patient. In spite of this variability among patients the mean of the means for the two drugs was of the same order of magnitude. If an arbitrary concentration of 1 mg. per 100 ml. was used as a desirable level for the minimal value for the week, it was achieved 73% of the time by sulfamethoxypyridazine and only 60% of the time by sulfadimethoxine. Since these studies were not done as a controlled study, the significance of such a small difference is minimal. However it is clear that there is no support for our hope that sulfadimethoxine would offer a greater margin of safety. Hence with this drug as with the earlier analogue it is recommended that the serum concentration obtained be measured after several weeks of treatment, and if it is below 1 mg. per 100 ml. the drug should be given twice a week.

In the study with sulfamethoxypyridazine the effectiveness was not demonstrated, because of the lack of beta hemolytic streptococci in the environment. Johnson, Mathews and Stollerman, however, have assayed this factor[4]. In this study, because a small outbreak of streptococcal disease occurred in the personnel, the patients were subjected to a real risk. In this situation they fared better than untreated patients. However, this exposure was not a severe stress, since antistreptolysin titers did not rise in either group of patients and no acute rheumatic fever episodes occurred.

In this study, 2 allergic type reactions occurred which required discontinuance of the drug. This may not represent any real difference from the results with sulfamethoxypyridazine, even though no patients developed reactions that required its discontinuance in more than twice the period of observation, since this was not an alternate patient controlled study.

TABLE 3.—COMPARISON OF RESULTS PREVIOUSLY OBTAINED WITH SULFAMETHOXYPYRIDAZINE COMPARED WITH THOSE FROM THIS STUDY WITH SULFADIMETHOXINE

			(Weekly Sulfonamide Concentration)*			
	No. of Pts. with Multiple Observations	*No. of Determinations*	*Range of Means for Each Patient mg./100 ml.*	*Mean ± S.D.*	*Determinations Below 1 mg./100 ml.*	
Drugs				*Mean*	*No.*	*%*
Sulfamethoxypyridazine	27	247	0.3–5.0	1.8 — 1.4	67	27
Sulfadimethoxine	25	114	0.4–3.3	1.3 — 0.5	45	40

*Sulfamethoxypyridazine in plasma; Sulfadimethoxine in serum.

Summary. (1) Sulfadimethoxine was given to 28 patients in a rheumatic fever convalescent home in a dose of 30 mg. per kg. weekly. Among the 25 patients who had 3 or more weeks of therapy, the mean minimal serum concentration measured just before each subsequent dose ranged from 0.4 to 3.3 mg. per 100 ml. The means were relatively constant for each patient and some patients had consistently higher values than others. Forty per cent of all the concentrations were less than

1 mg. per 100 ml. In all except 7 patients values were this low; in some, all were below this level, and in the rest a variable number were similarly inadequate.

(2) A small outbreak of group A beta hemolytic streptococcal disease occurred in the personnel near the end of the study. In 74 patient-weeks of observation there was one transitory infection among the treated patients. There were 40 patient-weeks in untreated patients at the same time with 4 infections. In the personnel there were 7 positive cultures in 104 weeks of observations. In the patients there were no rises in antistreptolysin titer or recurrences of rheumatic fever.

(3) Two patients developed skin rashes and systemic symptoms that necessitated discontinuance of the drug.

(4) These results are compared with those previously reported in the same institution for sulfamethoxypyridazine.

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SUMMARIO IN INTERLINGUA

Le Uso de Sulfadimethoxina in le Prevention de Infectiones Streptococcic in Patientes Rheumatic

1. Sulfadimethoxina esseva administrate a 28 patientes de un asylo pro convalescentes ab febre rheumatic in un dosage de 30 mg per kg de peso corporee per septimana. Inter le 25 patientes qui recipeva le therapia durante 3 septimanas o plus, le valor medie del minimos del concentration seral determinate justo ante omne dose subsequente variava inter 0,4 e 3,3 mg per 100 ml. Le valores medie esseva relativemente constante in le patientes individual. In certe subjectos illos esseva uniformemente plus alte que in alteres. Quaranta pro cento de omne le concentrationes mesurate esseva infra 1 mg per 100 ml. Solmente 7 patientes habeva nulle determinationes infra ille nivello. In plure casos, omne le determinationes esseva infra illo. In le remanente patientes, un numero variabile de determinationes reflecteva ille inadequatia.

2. Un minor eruption de morbo streptococcic hemolytic beta gruppo A occurreva in le personal del institution verso le fin del studio. In un total de 74 septimanas-patiente de observation, un caso transitori de infection occurreva inter le tractate patientes. Durante le mesme tempore, 40 septimanas-patiente de observation resultava inter le non-tractate patientes in le constatation de 4 infectiones. Inter le membros del personal, 7 culturas positive esseva obtenite in 104 septimanas-individuo de observation. In le patientes, nulle augmento esseva notate in le titros de antistreptolysina. Nulle recurrentia de febre rheumatic esseva constatate.

3. Duo patientes disveloppava un rash cutanee e symptomas systemic que rendeva necessari le discontinuation del droga.

4. Iste resultatos es comparate con illos previemente reportate ab le mesme institution pro sulfamethoxypyridazina.

MALIGNANT DISEASE IN THE AGED: REVIEW OF 16 YEARS' EXPERIENCE IN A MODERN MEDICAL FACILITY FOR THE ELDERLY

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AND

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The management of malignant disease in elderly patients is assuming ever greater importance as the proportion of older people in our population increases. There is no uniformity of opinion as to therapy in these conditions. Points of view are frequently expressed varying from an aggressive approach with prophylactic radical therapy for premalignant lesions such as colonic polypi, to the opposite extreme of no therapy or, at most, palliative control of symptoms because "cancer grows so slowly in old people."

This study was prompted by a desire to define the problem: to delineate the importance of malignant disease in an institutional group of elderly patients as a cause of morbidity and mortality; and to ascertain the possibility of efficacious treatment of these lesions in such patients. The study was made possible by the records and experiences at the Central House Unit of The Home for Aged and Infirm Hebrews of New York, where a group of older men and women receive thorough medical supervision during their lives and where an 80% incidence of postmortem examinations permits a final evaluation of their illnesses and of the treatment administered.

During the period covered by this study the census of the Central House has varied between 510 and 529 patients. The youngest present resident is 61 and the oldest is 98. Residents are admitted in all stages of health, varying from those who are vigorous and can live in apartment residences maintained by the home to those who suffer from chronic illnesses of great severity requiring continuous medical and nursing supervision. Most of these illnesses are cared for at the Central House Unit. The only significant exception is major surgery, which is performed in cooperating general hospitals. These patients return to the Central House for convalescence and their further life. The average life expectancy after admission to the Central House Unit is 4 years, 198 days.

Method. The necropsy protocols and clinical records for all residents who died at the Central House from 1942 through 1958 were reviewed. Those who had evidence of malignancy at time of death and those who had been treated for malignant disease during life were selected for study. The records were then analyzed to attempt to answer the following questions:

1) What was the relative incidence of malignant disease as a cause of death and as an incidental finding in persons dying of other diseases?
2) How often was the diagnosis established prior to death?
3) Was the diagnosis established sufficiently early to permit curative treatment?
4) In those patients dying without antemortem diagnosis of malignancy, did symptoms exist that should have indicated the necessity for further studies?

5) Was the lesion treated and by what means?
6) If untreated, what were the reasons?
7) Did treatment result in cure or give significant relief of symptoms?
8) What routine studies would be most valuable in detecting the onset of treatable malignancy?
9) What was the effect of advanced age on symptoms and clinical course of malignant disease?

Results. INCIDENCE. From the opening of the laboratory facilities of the Central House in 1942 until January, 1958, there were 730 postmortem examinations; 310 (42.5%) in men and 420 (57.5%) in women. Of these patients, 119 (16.3%) had malignant disease. Forty-four (37%) of them were men and 75 (63%) were women. The incidence of malignant neoplasms in the male deaths was thus 44 in 310 or 14%, and in female deaths 75 in 420 or 18%. The average age at death of this group of people was 80.1 years. The youngest was 64 and the oldest 94.

The organs involved are noted in Table 1. Carcinoma of the gastrointestinal tract is seen to comprise 50% of the malignancies. The incidence is similar in male and female patients. The stomach and the colon including the rectum are each responsible for the same number of cases: approximately 19% of the total for each. The genitourinary system accounts for 16%, the lungs 13% and the breast 11%. The incidence of breast malignancies in women alone is 17%. Other sites each account for but a few cases. It is of

TABLE 1.—SITE OF MALIGNANCY IN 730 POSTMORTEM EXAMINATIONS. THE CENTRAL HOUSE UNIT OF THE HOME FOR AGED AND INFIRM HEBREWS OF NEW YORK CITY

Site	*Male*	*Female*	*Total*	*%*
G.I. TRACT	26	33	59	49.6
Esophagus	1	0	1	0.8
Stomach	10	13	23	19.3
Duodenum	1	0	1	0.8
Colon	5	8	13	10.9
Rectum	3	6	9	7.6
Pancreas	1	3	4	3.4
Biliary System	1	3	4	3.4
Liver	4	0	4	3.4
G.U. SYSTEM	7	12	19	16
Prostate	2	0	2	1.7
Bladder	5	1	6	5.0
Kidney	0	2	2	1.7
Ovary	0	5	5	4.2
Uterus	0	4	4	3.4
Breast	0	13	13	10.9(17*)
Lung	7	7	14	11.7
Tonsil	0	1	1	0.8
Thyroid	0	1	1	0.8
Skin (Melanoma)	1	1	2	1.7
Leukemia	2	1	3	2.5
Lymphosarcoma	0	3	3	2.5
Bone	1	1	2	1.7
Metastatic (No primary noted)	0	2	2	1.7
TOTAL	44(37%)	75(63%)	119(100%)	

*% of female patients

interest that in this group there are but 2 cases of grossly obvious carcinoma of the prostate sufficient to be of clinical significance.

MORTALITY. Ninety-one patients (76.5%) of the total died of the malignancy. In 23.5%, death was from other causes and the malignancy was either under control from treatment or was an incidental postmortem finding. It is thus obvious that carcinoma is a significant cause of death in elderly patients: 12.5% of all deaths in this group of patients were directly due to this disease.

MULTIPLE TUMORS. Thirteen patients, 11% of those with cancer, had more than one malignant tumor during their life-time. The second tumor arose anywhere from 1½ to 36 years after the first. In this study, they were classified by the lesion responsible for their death. Three of these patients had previous treatment of carcinoma of the breast by radical mastectomy and many years later two of them developed carcinoma of the other breast. One died of a carcinoma of the colon. Six patients had been successfully treated for epitheliomas of the skin some time prior to the development of a visceral malignancy. Two patients had leukemia in addition to other carcinomas. One patient had two simultaneous bowel lesions. One had a carcinoma of the ovary in addition to a carcinoma of the uterus, another patient a carcinoma of the pancreas in addition to a carcinoma of the stomach. These 14 malignancies occurred in 13 patients since one patient had three lesions.

Clinical Features. DIAGNOSIS. An outstanding feature of these cases is a lack of symptoms early in the course of their disease. These patients are accustomed to a variety of aches and pains and so pay little attention to new ones. It is even possible that sensitivity to pain is decreased in older people. Many of the patients had some degree of cerebral damage, most often on an arteriosclerotic basis, that further complicated the obtaining of a valid history. It is therefore understandable that the most common initial symptoms recorded were weight loss and anemia. These frequently preceded any other symptoms for a period of years. The average duration of unexplained weight loss before other symptomatology, in the 21 patients for whom it was the first manifestation of illness, was 2 years. Similarly, a secondary anemia was the initial manifestation of illness in 16 patients and preceded any other symptoms for an average of 15 months.

TABLE 2.—PRINCIPAL EARLY SYMPTOMS NOTED IN 119 ELDERLY PATIENTS WITH CARCINOMA

Symptoms	*Number*	*%*
Weight Loss	52	44
Mass	47	39
Anemia	42	35
Pain	36	30
Melena	24	20
Anorexia	19	16
Diarrhea	12	10
Vomiting	8	7
Urinary Complaints	7	6
Vaginal Bleeding	6	5
Constipation	5	4
Jaundice	5	4
Low grade fever	5	4
Cough	4	3
Hemoptysis	2	2
Hematemesis	1	1

The principal initial symptoms are listed in Table 2. The nonspecific nature of the more frequent manifestations is quite apparent. The lesson to be learned is obvious. Anemia and loss of weight in elderly patients indicates the need for radiographic study. The high incidence of melena pleads for routine examinations of stool for occult blood.

In spite of the difficulties, a correct diagnosis of the patient's disease was

established prior to death in 79 (66%) of the patients. In 6 others, a diagnosis of intra-abdominal malignancy was made, but the site was incorrectly specified. These were: a patient with a carcinoma of the duodenum, 2 with carcinoma of the pancreas, one with a carcinoma of the gallbladder, one with a carcinoma of the common bile duct, and one with a primary carcinoma of the stomach with hepatic metastases and obstructive jaundice due to either metastatic disease or to a carcinoma of the pancreas.

This leaves 34 patients, 29% of the total, who died without a proper diagnosis. Eleven were essentially asymptomatic until death from an intercurrent illness. Six patients died very rapidly after their admission to the Central House before studies could be completed. Five patients had mental aberrations that precluded sufficient cooperation for studies. In but 12 cases would a more vigorous approach such as routine roentgenographic studies have yielded a greater salvage.

TREATMENT. Forty-two malignancies (35%) were treated actively. Surgical extirpation, Roentgen-ray irradiation, physical destruction of the tumor by coagulation or fulguration and hormone therapy were all used. Fifteen of the patients received more than one modality. The primary therapy in 23 cases was surgical excision of the lesion; in 10, intensive irradiation with Roentgen-ray or radium; in 7, chemotherapy and in 2, fulguration of the tumor.

As one would expect, the best long-term results were achieved in the patients treated by surgery, although long-term survivals were achieved by radiation of lymphomas and by hormone treatment of malignancies of the breast and prostate. Local fulguration of a tumor of the bladder gave a long-term arrest, whereas similar treatment of a rectal lesion was followed by prompt local and later systemic recurrence and death.

The average duration of life of the treated cases was 5.4 years. Eleven patients (25% of the treated group) were free of evidence of malignant disease at necropsy after death from another illness. In 13 patients, 31% of the treated group, the disease did not appear to be influenced by the treatment. The remaining 18 patients achieved significant palliation for an average of 4 years before succumbing to recurrent disease.

Seventy-nine patients were not treated for their tumors. In 34 instances, a diagnosis was not established. Seventeen of these patients had no symptoms from their tumors. Twenty-seven patients had advanced lesions at the time of diagnosis so that treatment would have been futile. Ten patients were so ill from advanced cardiovascular, renal or cerebral diseases as to be considered untreatable. Eight patients refused surgical therapy.

Postmortem examination disclosed that of the 79 patients untreated, 11 still had localized disease at the time of death and could have been treated successfully.

DURATION OF THE DISEASE. An attempt was made to determine the time of onset of the disease or at least the time of advent of the earliest symptoms and so to estimate the total duration of illnesses. The errors are obvious and it must be assumed that the duration of illness so determined, is merely a minimum value. There was considerable variation in the duration of disease with the site of the primary tumor. Since the longer durations were noted in locations where symptoms appear earlier, this confirms the impression of prolonged silent intervals in these diseases. The overall average duration of life after the first appearance of symptoms of malignancy was 3.4 years. The

duration for sites with a significant number of cases (10 or more) is shown in Table 3. The duration varies from one year for the biliary tract to 10 years for the breast. This latter prolonged survival is particularly noteworthy.

TABLE 3.—DURATION OF LIFE FROM ONSET OF SYMPTOMS FOR VARIOUS SITES

Site	*Treated Cases Years*	*Untreated Cases Years*
Stomach	6	3.5
Colon and Rectum	6	2.5
Biliary Tract and Pancreas	—	1.5
Urinary Tract	4	1.0
Genital	2	1.5
Breast	10	—
Lung	—	2.0

The range of longevity after onset of symptoms does not support the contention that malignancy in elderly people is relatively benign but rather indicates that these illnesses, if not identical, are comparable at all ages.

PREVIOUS STUDIES. Studies of the incidence of carcinoma in old age have been made by Howell and Piggot[1], Monroe[2], and Mulligan[3]. Although these studies differ somewhat from the present study in that the cases reported came from the services of general hospitals rather than from a residence home, it is nevertheless of interest to compare the results. The present series is probably more representative of the situation in the general population, although there is undoubtedly substantial selection of material even in this group. Zeman[4] made similar studies but has not published them. He has kindly made his data available for comparison. He studied the necropsy findings in 700 people 60 years of age and over at The Mount Sinai Hospital in New York City from the year 1933 to 1941. He noted an incidence of carcinoma of 223 cases in 700 necropsies (32%). Twenty-seven of these tumors (4%) were merely incidental necropsy findings and not related to the cause of death.

Howell and Piggot[1] studied 2,221 necropsies in patients aged 65 or over at the St. John's Hospital, London, England. They found a 28.2% incidence of new growths (624 cases).

Monroe[2], in 1951, published a comprehensive study of disease in old age. He reviewed the records of 7,941 individuals over the age of 61 years who entered the out-patient or in-patient medical service of the Peter Bent Brigham Hospital in Boston, Massachusetts, from March, 1913, to March, 1943. Neoplastic lesions were discovered in 1,110 patients (13.9% of the total). The necropsy incidence was 24.2% and the clinical incidence alone, without necropsy verification, was 12.0%.

Mulligan[3] in 1959 reviewed the necropsy protocols over a 15-year interval from 1940 to 1955 at the Colorado General Hospital. There were 257 cancer patients 70 years of age or older. This represented 22.6% of all necropsies during this time. There were an additional 25 incidental cancers (2.2%) that did not contribute to the patients' deaths.

The higher necropsy incidence in all these series than our 16% is to be explained by the fact that all of these series emanate from general acute hospitals. The lower clinical incidence in Monroe's series is partially explicable by incomplete clinical diagnoses but is also attributable in part, to the fact that the clinical group contains patients who are still living (and may later develop malignancies before they die).

Table 4 shows the relative rates for different sites in each of those series. The relative incidences are quite comparable; the differences noted are probably within sampling error.

In all the series, the gastrointestinal

tract was responsible for more than half of the tumors. In this system, the stomach was the most frequent site with from 14% to 23% of all lesions and the colon, including the rectum, second with from 13% to 27%. The occasional marked discrepancies are explicable by the source of the data. Thus the absence of deaths due to carcinoma of the breast in Zeman's study is accounted for by the fact that obvious terminal malignancies are not admitted to the hospital in question. Patients who are treated for breast carcinoma at that hospital die elsewhere. Mulligan's series is distorted by a predominence of male patients, the ratio of males to females was 2.95 to 1. This partially accounts for the grossly higher incidence of prostatic carcinoma and the very low incidence of breast and uterine carcinoma.

Discussion. We can now return to our original questions and see how they have been answered. Sixteen per cent of those dying at the Central House had evidence of malignant disease at time of death or prior to death and three-fourths of these or 12% of the entire group, died of the malignant disease. Diagnosis was established prior to death in two-thirds of the patients and could have been made in another 8%. In a little over a third of the patients diagnosis was established at a time when treatment could be insti-

TABLE 4.—RELATIVE INCIDENCE OF MALIGNANT DISEASE AT VARIOUS SITES

	% Incidence				
Site	*Howell & Piggot*	*Monroe*	*Zeman*	*Mulligan*	*This Series*
G.I. TRACT	58.1	51.9	64.0	44.9	49.6
Esophagus	9.1	3.1	1.7	1.5	0.8
Stomach	17.4	23.3	19.2	13.8	19.3
Colon	16.4	11.5	19.0	7.7	10.9
Rectum		3.8	8.5	5.4	7.6
Pancreas	4.6	5.0	7.6	6.9	3.4
Biliary Tract	6.6	3.8	7.1	7.7	3.4
Liver	2.4	0.8	0.9	1.1	3.4
Duodenum	—	—	—	0.4	0.8
Small Intestine	1.6	0.6	—	0.4	—
GENITOURINARY	14.0	22.0	15.2	22.6	16.0
Penis	0.1	—	—	0.4	—
Prostate	3.4	10.5	4.9	13.1	1.7
Bladder	3.0	5.5	6.7	4.2	5.0
Kidney	2.4		2.6	1.9	1.7
Ovary	2.6	6.0	0.5	1.5	4.2
Uterus	2.4		0.5	1.5	3.4
Testes	0.1	—		—	—
Breast	2.6	6.7	—	2.3	10.9
Lung	14.4	6.2	10.3	8.4	11.8
ENT	3.3	1.8	2.2	3.8	0.8
Thyroid	—	0.5	0.5	1.1	0.8
Skin	0.1	2.2	0.5	3.1	1.7
Lymphoma	0.6	—	2.3	4.6	5.0
Bone	0.1	0.7	—	—	1.7
Other	6.8	8.0	5.0	9.6	1.7

tuted with some success. In another third, earlier diagnosis might have permitted more vigorous treatment. Treatment gave significant palliation in two-thirds of those treated and resulted in cure of the disease in one-fourth of those treated. The best results were obtained in carcinomas of the gastrointestinal tract and breast.

Symptoms are often vague and nonspecific in elderly patients. They cannot be differentiated from the ubiquitous minor aches and pains afflicting these people. Early diagnosis depends upon routine measurements of weight, blood hemoglobin concentration, erythrocyte sedimentation rate, and occult blood in the stool, followed by intensive investigation of those patients showing abnormalities on these determinations. Such a program should give significant increments of longevity and comfort to this population, since adequate treatment can be accomplished safely and is relatively successful.

The management of elderly patients is a complex process. In these instances, to an even greater degree than younger patients, the physician must consider his entire patient and not merely an individual disease. These patients can not be considered as examples of given diseases, for they all demonstrate the result of the action of various pathological processes over variable periods of time. The effect of all of them must be evaluated in their relationship to contemplated therapy.

The therapeutic goal must be clearly defined. When there is a choice, shall we seek to prolong life or to increase comfort? There are not any neat solutions. Each case requires the exercise of that nicety of judgment which is the result of both conscious and subconscious evaluation of a multitude of variables and the evaluation of ill-defined conflicting probabilities. The basic data that permit these evaluations, when it is anything in addition to clinical impression, must be the sort of summation and statistical evaluation of the results of management and treatment of patients such as those herein presented. The facts and individual observations always exist but the summation gives them a certain concreteness that assists our reasoning.

Summary. The incidence and results of management of malignant disease in a home for the aged has been reviewed. Sixteen per cent of patients dying at the Central House Unit of The Home for Aged and Infirm Hebrews of New York had evidence of malignant disease prior to death or at postmortem examination. Three-fourths of them died of the malignancy. Tumors of the gastrointestinal tract comprised 49.6%; the genitourinary tract, 16%; the lungs, 11.9% and the breast, 10.9%. Diagnosis was established prior to death in two-thirds of the patients. In a little over one-third of the patients, diagnosis was established early enough to permit treatment with some hope of success. Treatment gave significant palliation in two-thirds of those treated and resulted in cure of the disease in one-fourth of those treated.

This study indicates the need for simple screening tests, such as blood and stool examination, and frequent weight measurements in older individuals. The excellent response to therapy in many of our cases emphasizes the value of early aggressive therapy even at advanced ages.

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SUMMARIO IN INTERLINGUA

Morbo Maligne a Grande Etates
Revista de 16 Annos de Experientia in Un Moderne Installation Medical pro Ancianos

Es revistate le incidentia e le resultatos del tractamento de morbo maligne in un asylo pro ancianos. Dece-sex pro cento del patientes moriente al Casa Central del Home pro Ancian e Infirme Hebreos a New York manifestava evidentia de morbo maligne ante le morte o al necropsia. Tres quartos de istes moriva per le malignitate. Tumores del vias gastrointestinal representava 49,6%, del vias genitourinari 16%, del pulmones 11,9%, e del pectore 10,9%. Le diagnose esseva establite ante le morte in duo tertios del casos. In levemente plus que un tertio, le diagnose esseva establite satis precocemente pro permitter le initiation de un curso therapeutic con alicun spero de successo. Le tractamento effectuava grados significative de palliation in duo tertios del casos tractate e resultava in un curation in un quarto de istos.

Iste studio indica le desiderato de un simple test de detection, per exemplo le examine de sanguine e feces, e frequente mesurationes del peso de subjectos de etate avantiate. Le excellente responsa al therapia in multes de nostre casos illustra le valor de un prompte e aggressive therapia mesmo in patientes de grande etate.

INCIDENCE OF HYPOTHYROIDISM IN MORE THAN ONE MEMBER OF A FAMILY

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The clinical manifestations of thyroid deficiency in humans are so extensive and complex that investigation of any one area seems, unavoidably, to lead to the discovery of new unexplained facts and speculations which warrant additional study. Such a sequence of events recently occurred during an investigation of the incidence and diversity of symptoms associated with early or "partial" hypothyroidism as described by Starr and colleagues[21, 22]. Each patient with proven or suspected thyroid deficiency was requested to complete a questionnaire listing fifty-two of the symptoms that might occur in the protean hypothyroid-hypometabolic state. Final tabulation of the symptoms reported in the questionnaire were informative. They tended to confirm the clinical impression that psychodynamic symptoms such as nervousness, tension, mood swings, irritability, feelings of inadequacy, frustration, and multiple phobias, though uncommonly stressed in the textbook picture of hypothyroidism, are as common as complaints of fatigue and lethargy. An unexpected finding which eventually led to a new investigation came from the frequently volunteered statements that several of these patients' spouses had many of the same complaints and should be investigated along similar lines. On following up such suggestions, it was found that among 123 cases of well-documented hypothyroidism attending the clinic, varying degrees of thyroid deficiency existed in either husband or wife or parent and child in 15 of 57 (26%) families. The purpose of this report is to present the laboratory data related to thyroid function studies in these families and to discuss the possible etiology and significance of the findings.

Methods and Materials. Interested in what seemed to be a significant and previously unreported incidence of hypothyroidism occurring in more than one member of a family, an attempt was made to contact and screen all available members of a family once a diagnosis of hypothyroidism was established in one member of the family. Such an undertaking presented more difficulties than anticipated, and although there were 108 hypothyroid patients in the original clinic series, it was possible to contact and evaluate only 57 families. Of this number, hypothyroidism was diagnosed in more than one member in 15 families.

The patients ranged in age from 15 to 50 years as shown in Table 1, patients beyond the fifth decade being uncommon in an overseas military population. The period of observation and treatment varied from 4 to 22 months with an over-all average of 10.5 months per patient. To insure the accuracy of a diagnosis of hypothyroidism, no patient was included in this series who did not obtain a satisfactory response, both objectively and subjectively, to properly administered thyroid hormones (desiccated thyroid or l-triiodo-thyronine). An additional 9 patients who were clinically thought to be hypothyroid by myself or my colleagues were likewise excluded because of equivocal pre-treatment laboratory data not fully documenting the diagnosis.

A diagnosis of hypothyroidism was determined by: 1) an initial interview during which a comprehensive history was taken and a thorough physical examination made.

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with special emphasis on findings pertinent to the metabolic status of the patient, such as thyroid enlargement or the delayed ("hung-up") character of the Achilles tendon reflex; 2) protein-bound iodine (PBI) levels determined by a modified Barker technique, using both a baseline blood sample and a second sample drawn 24 hours after the intramuscular injection of 10 international units of a potent thyrotropic hormone preparation*; 3) an electrometric recording of the free Achilles tendon reflex as measured by the kinemometer, an apparatus devised and reported on in the medical literature by Lawson[15], and employed in our clinic since shortly after the appearance of Lawson's report; 4) determination of the serum cholesterol and basal metabolic rate (BMR) by standard techniques.

Although not incorporated into the thyroid-metabolic work-up of the average patient, the following laboratory results, when carried out with another diagnosis in mind, were often of value in suggesting the possibility of hypothyroidism: flat oral glucose tolerance test (Kupperman and Epstein[13]), low voltage electrocardiogram (Starr and Liebhold-Schuechk[23]), vaginal smear with subnormal estrogen effect, low urinary 17-ketosteroids in females, and sluggish sperm motility on sperm analysis in males (Farris and Colton[9]).

INTERPRETATION OF THYROID FUNCTION TESTS. Previous experience with several hundred PBI determinations done in our laboratory has led to the acceptance of 4.0 to 8.0 μg. as the normal range for euthyroidism. A further aspect to the interpretation of the PBI value has been the finding that, although a PBI reported in the normal range in a case later shown to be unequivocally hypothyroid is not uncommon, the converse: namely, a low PBI in a patient who otherwise lacks the clinical features of hypothyroidism or fails to make the expected response to adequate thyroid hormone replacement, or both, is decidedly rare. It is therefore our practice to accept a PBI below 4.0 μg. as suggestive evidence of hypothyroidism, while a PBI of 4.0 μg. or above in a clinically suspect individual is under suspicion of occult iodine contamination unless there is a rise of 1.5 μg. or more in the PBI following thyrotropic hormone (TSH) (Bishopric, Garrett and Nicholson[1], Schneeberg, Perloff and Levy[19]). An alternate explanation for the PBI above 4.0 μg. which fails to respond significantly to TSH is offered by the work of Jeffries *et al.*[12] dealing with "low thyroid reserve." In general, however, the lack of thyroid reserve is believed to be uncommon in the patient who has not undergone prior treatment with radio-iodine$_{131}$ or thyroid surgery. Considering that sources of iodine contamination of the PBI are regrettably numerous (various Roentgen-ray contrast media, medications containing iodine; common use by the military services of iodine-containing pills to decontaminate the drinking water during field problems), it is believed that the patients listed in Table 1 with normal baseline PBIs but whose PBIs failed to rise 1.0 μg. or more post-TSH, probably represent cases of primary, rather than "low reserve," hypothyroidism. The TSH used was determined to be potent by testing each batch on 5 controls: the average rise in PBI being 2.6 μg. post-TSH with a range of 1.8 to 4.0 μg.

Experience with the Lawson kinemometer has shown it to be an accurate and rapid means by which one can screen patients for hypothyroidism and "euthyroidal hypometabolism" (Kurland, Hamolsky and Freedberg[14]), and has proven of immeasurable value as a diagnostic and prognostic device, ideally suited for a busy outpatient clinic. A second report by Lawson[16] comparing the duration of the contraction phase (S-D interval) of the Achilles reflex with the existing thyroid status of the patient as pre-determined by more conventional parameters of thyroid function, has demonstrated an accuracy of 94% in diagnosing hypothyroidism.

A comparison of the S-D interval of the kinemometer with the results of the PBI response to TSH in 84 cases of suspected hypothyroidism have, likewise, shown a high degree of accuracy, well over 90%, in distinguishing between euthyroid and hypothyroid patients. It has been my experience, however, that the S-D interval prolonged beyond the normal range of 140 to 240 milliseconds (as measured on ordinary electrocardiographic paper) is not specific for hypothyroidism since it also occurs in "euthyroid hypometabolism"[10] and is, in fact, the best available objective criterion that can be employed in the diagnosis of that condition. For this reason, it is probable that the state of the tendon reflex is a qualitative measure of the peripheral or end-organ response of the body to thyroid hormones rather than a reflection of the output of active hormone by the gland itself. The kinemometer recording is similar in this respect to the BMR and serum cholestrol, but has the added advantage of being

*Supplied as Thyreostimuline by the Endopancrine Laboratories, Paris.

TABLE 1.—RESULTS OF THYROID FUNCTION TESTS IN 15 FAMILIES

Patients: Number, Initials, Relationship: (H=husband, W=wife, C=child)	*Age*	*PBI before TSH (μg.)*	*PBI after TSH (μg.)*	*BMR (normal range −10 to +10)*	*Kinemometer reading (millisec.) (normal range: 140 to 240 millsec.)*	*Serum Cholesterol (mg.) (normal range 150 to 250 mg.)*	*Remarks**
1. K.K.(H)	45	2.8	3.3	——	280	350	hypertension,* obesity*
P.K.(W)	37	4.0	4.0	−17	250	250	symptoms followed third pregnancy
2. C.C.(H)	33	4.0	5.0†	——	220	235	on thyroid R_x past year. multiple allergies, mood swings
H.C.(W)	31	5.0	4.8	−15	260	270	endometrial hyperplasia severe pre-menstrual tension*
3. K.A.(H)	33	3.5	4.3	−22	250	240	nervousness,* palpitations* "neurasthenia"*
J.A.(W)	29	4.0	3.3	−10	265	290	thyroid enlargement,* cancer phobia*
4. B.S.(H)	45	4.0	4.4	−8	260	330	hair loss,* myalgias*
S.S.(W)	39	3.5	3.1	−15	250	260	obesity, hypertension* infertility
5. W.B.(H)	50	2.8	3.5	−14	260	300	nervousness,* seborrhea of scalp*
B.B.(W)	44	4.2	4.5	−20	265	230	obesity,* pre-menstrual tension*
6. C.C.(H)	42	4.0	5.2	−15	300	280	functional G-I symptoms*
A.C.(W)	35	3.8	4.4	−18	250	240	previous psychiatric treatment, phobias*
7. P.B.(H)	38	3.2	3.8	−8	270	320	obesity,* hair loss*
A.B.(W)	35	3.3	3.0	−24	280	260	insomnia,* menorrhagia*

A.B.(W)	35	3.3	3.0	—24	₴80	₴80	
8. A.C.(H)	47	4.0	4.2	——	₴60	300	recurrent bursitis,* poor memory*
M.C.(W)	42	2.0	1.9	—15	₴40	₴40	hypertension,* pre-menstrual tension*
S.C.(C)	15	2.4	2.2	—28	₴70	₴20	short stature, dysmenorrhea* irregular menses*
9. J.H.(H)	45	5.0	5.0	—7	₴50	330	relative impotence*
M.H.(W)	43	4.2	4.0	—18	₴70	₴60	infertility,* menorrhagia*
10. P.W.(H)	49	3.4	3.5	——	₴60	₴80	failing memory,* impotence*
P.W.(W)	45	3.2	3.5	—22	₴50	₴40	hysterectomy for menorrhagia, previous unexplained infertility.
11. G.H.(H)	₴9	4.2	4.3	—24	₴60	340	frequent URIs,* oligospermia, decreased motility*
B.H.(W)	₴5	3.5	4.0	—12	₴50	₴00	chronic backache*
12. E.P.(H)	30	4.0	4.4	—10	₴60	350	decreased libido,* obesity
F.P.(W)	33	3.8	3.5	—19	₴80	₴00	thyroid nodule,* infertility, domestic difficulty*
13. S.W.(W)	47	6.3	5.9	—26	₴60	300	obesity,* hypertension*
S.W.(C)	15	3.2	3.7	+3	₴40	₴50	thyroid nodule,* behavior problem*
14. G.R.(H)	44	4.0	4.5	——	₴50	400	obesity* hypertension.
F.R.(W)	40	3.0	3.5	—15	₴75	₴40	nervousness, numerous phobias, lethargy,* under care of psychiatrist.
15. V.W.(H)	46	₴.8	3.0	—8	₴70	₴85	severe backache* and arthralgias*
E.W.(W)	40	₴.7	—	—26	₴80	₴65	habitual aborter (5);* no GYN pathology.

†PBI post-TSH drawn in 48 hours rather than ₴4 hours since patient on thyroid.
*Symptoms or states probably secondary to hypothyroidism and relieved by thyroid hormone therapy.

unaffected by emotional stimuli which could alter the BMR, or systemic factors (such as hepatic or biliary disease) which could elevate the total cholesterol.

My belief in the superior accuracy of the kinemometer in comparison to the BMR is further strengthened by results obtained in 10 patients who had both kinemometer tracings and BMRs recorded on 3 consecutive days. Although the S-D interval of the kinemometer varied less than ± 10 milliseconds, the BMR in 7 out of 10 cases dropped significantly on each succeeding day, with the last reading most closely approaching the estimated metabolic status of the patient and comparing best with the kinemometer value. In view of such experiences, and because of convenience to the patient, the kinemometer is used to gauge the metabolic response of patients put on either desiccated thyroid or l-triiodothyronine in preference to the BMR or serum cholesterol.

Results. The results of the laboratory data and pertinent clinical symptoms of each of the 31 patients included in this study and who made up the 15 family groups are presented in Table 1. Baseline PBIs ranged from 1.9 to 5.9 μg., with an average value of 3.45 μg. for the group. The PBI response 24 hours post-TSH ranged from 0 to 1.2 μg., with an average rise of 0.28 μg. Since patient C.C. had been taking thyroid for the past year, the second PBI was drawn 48 hours post-TSH rather than 24 hours and it is the 48-hour value which is shown in Table 1. Initial BMRs in 28 patients ranged from −28% to +3%, five results being in the normal range of −10% to +10%. The BMR value for the group as a whole averaged −15%. The S-D interval of the kinemometer was prolonged beyond 240 milliseconds in 27 of 30 patients, ranging from 240 to 300 milliseconds and averaging 260 milliseconds for the group. Serum cholesterols varied from 200 to 410 mg. with 19 out of 30 values above 250 mg. The average cholesterol was 278 mg. for the entire group.

Treatment of the hypothyroid state consisted of desiccated thyroid in average daily maintenance doses of 150 to 180 mg. in 19 cases and l-triiodothyronine in average daily amounts of 100 to 125 μg. in 12 cases. The latter group consisted of patients with thyroid enlargement, obesity, or infertility problems and were given l-triiodothyronine in an investigatory capacity.

Post-treatment PBI values in the 19 patients treated with desiccated thyroid ranged from 4.5 to 7.3 μg., the average being 5.8 μg. Since triiodothyronine lowers PBI, this parameter cannot be employed to measure metabolic response. What is believed to be an optimum S-D interval of 200 milliseconds was sought in all cases and achieved in 25 of 31 cases. For reasons previously mentioned, BMRs were not routinely used to follow patients on thyroid hormone therapy. Of the 19 patients with pre-treatment serum cholesterols above 250 mg., serial or repeat cholesterols were performed in 15. Following therapy, serum cholesterol levels decreased 30 mg. or more in 14 and returned to normal limits in 12, the average fall in cholesterol being 45 mg. per patient for the group.

Over-all clinical improvement as judged by objective data and by subjective relief of symptoms believed to be secondary to thyroid deficiency were considered to be excellent in 17 patients (75% of symptoms relieved) and good in 14 patients (50 to 75% of symptoms relieved).

While the present series of cases is admittedly small, a statistical analysis is not required to recognize that the finding of hypothyroid states in 2 or more members of 15 families out of 57 families tested is highly significant. Whether or not such a high incidence (26%) exists among the families of patients with hypothyroidism at large can be proven or disproven only by the proper investigation of such families and by pooling the available data.

Discussion. Whether a state of par-

tial or mild hypothyroidism exists between the extremes of euthyroidism and frank myxedema and whether such a metabolic state not only exists but is both common and widespread, is, unfortunately, still an unsettled issue. It is hoped that the wide divergence of opinions regarding incidence of hypothyroidism in the population at large will be resolved in the near future. Lowrey, Ware and Starr[17], basing their conclusions on results of PBI determinations carried out on several thousand industrial workers in California, have estimated that no less than 5% of the entire adult population has some degree of thyroid deficiency. Our own experience in dealing with a military population of approximately 10,000 (and personal contact with about 20% of the potential case material) is somewhat less than Starr's estimate, but approached the incidence figure of 3 to 4%.

It is intriguing to speculate why an endocrinopathy which was previously considered to be uncommon should, in fact, be commonly encountered in everyday practice, especially in patients whose complaints are rather vague and involve several bodily systems, including the psyche. A possible explanation may be found in the recent work of Roitt and Doniach[18], and others (Witebsky, Rose and Shulman[24]) which convincingly established an auto-immune mechanism to released thyroglobulin and other thyroid antigens as the underlying etiology and pathogenesis of the majority of cases of chronic thyroiditis and spontaneous myxedema. Such findings are particularly pertinent to the cases under discussion for, after careful questioning of these patients, it was found that a bout of mumps had occurred in one or both members of 4 of the 15 families some 3 to 12 months before the onset of their hypometabolic symptoms. Since the mumps virus has been incriminated as an etiological agent in acute and subacute thyroiditis (Blattner[2]), it is conceivable that a subclinical thyroiditis was a manifestation of the mumps viremia, leading in time, via an auto-immune response to thyroglobulin-like substances released by the damaged follicle to lymphocytic invasion of the thyroid gland (struma lymphomatosa) and ultimate thyroid failure (Crile[6]).

An additional 2 patients gave a history of having had infectious hepatitis, and one patient, infectious mononucleosis, antedating their hypothyroid state by one to three years. The possible etiological significance of this finding is at present unknown.

It is regrettable that the various complement-fixation and tannic-acid treated red-cell agglutination tests for detecting circulating thyroglobulin antibodies (Blizzard *et al.*[3], Cline, Selenkow and Brooks[4], Doniach, Hudson and Roitt[8]) were not available for use in documenting the presence of autoimmunity in these patients. Such procedures offer a promising approach to the problem of placing the occurrence of hypothyroidism, both in families and in the general population, on a firm, logical footing, and should be employed to that end whenever possible.

Among the 15 families reported here, hypothyroidism was found to occur in husband and wife on 13 occasions, and parent and child in only 2, suggesting that the influence of inheritable factors, such as inborn errors in thyroxine synthesis (Hutchison and McGirr[11]), is probably not of etiological significance as the cause of hypothyroidism in these cases. It should, however, be mentioned that Doniach has observed a rather high incidence of thyroid abnormalities among blood relatives of patients with Hashimoto's disease, even though such relatives may live

some distance apart. Based on this observation, Doniach has suggested the possibility that a tendency for thyroid auto-immunity in response to an appropriate etiological agent which triggers the process may be an inherited abnormality (Doniach[7]).

That certain disease states now encompassed by the ever-widening spectrum of auto-immunity can be genetically linked seems well established by both allergists and hematologists working in their respective fields. Whether the allergy-prone individual is more susceptible to all, or even a majority, of auto-immune diseases is not known. It has been my experience that, in general, hypothyroid patients are often afflicted with multiple allergies—allergic rhinitis and other manifestations of respiratory allergies in particular—and it is likewise the experience of an allergist colleague of mine (Cowan[5]) that allergy patients, especially ones with atopic allergy, are frequently hypothyroid. Shambaugh, in a recent report on the successful treatment of Meniere's disease with l-triiodothyronine[20], has proposed an interesting hypothesis correlating the presence of allergy with thyroid dysfunction; the common denominator being cellular production of an abnormal type of enzyme.

Recognition of the occurrence of hypothyroidism among two or more family members has certain practical applications for the general physician. It is proposed that the family of an individual recently diagnosed as hypothyroid should be routinely screened for the existence of the same condition *especially* when the patient is seeking treatment for infertility, or when the patient reports severe marital discord.

In the case of infertile couples, it seems well established that thyroid deficiency can lower fertility potential and performance, and conversely, that there is a relatively high incidence of hypothyroidism among couples seeking medical advice for infertility. In my own experience, 9 members of 20 infertile couples (23%), all of whom were thoroughly studied both in regard to reproductive function and to metabolic status, showed evidence of hypothyroidism or "euthyroid hypometabolism" and benefited considerably from proper hormonal treatment with desiccated thyroid or l-triiodothyronine*[10]. With regard to married couples whose family life is gradually deteriorating because of continual quarreling and frustration due to metabolic as well as psychological factors, the situation may be considerably improved if the physician makes an effort to investigate and correct a state of thyroid hypofunction that may exist in either or both partners. A rather grim statistic revealed by the afore-mentioned thyroid questionnaires given to 123 patients with verified hypothyroidism concerns a query into the presence of "serious domestic difficulty bordering on or leading to divorce." Forty per cent of married patients reported either bordering on divorce or actually having one or more divorces *since the onset of their hypometabolic symptoms.*

The argument for keeping a diagnosis of hypothyroidism and "hypometabolism" in mind for the average patient seeking medical advice for his or her marital difficulties does not necessarily imply that such a diagnosis will commonly be made; nor that when hypothyroidism is found and corrected, such therapy will restore marital bliss along with euthyroidism. What is suggested, however, is the following considerations: 1) That the proper thyroid hormone when administered in adequate amounts to the hypothyroid or "hypo-

*Supplied as "Cytomel" by Smith, Kline & French Laboratories, Philadelphia, Pa.

metabolic" patient may, to some degree, help him or her to cope successfully with personal problems by alleviating the psychodynamic symptoms secondary to thyroid or metabolic deficiency. In this respect, the therapeutic response made by the patient with early hypothyroidism is no less gratifying to observe than the oftentimes dramatic response of the patient with myxedema; it may, in fact, be more rewarding, for it has been my experience that when hypothyroidism is diagnosed and corrected in its incipient stages, the ultimate response to thyroid replacement therapy is more complete, and therefore more satisfying, than when the disease has been allowed to progress for a few years and the patient has developed a super-imposed neurosis which is not always reversible. 2) For the individual in need of long-term psychotherapy who is also hypothyroid or "hypometabolic," proper thyroid hormone support will help considerably to further a positive response to psychotherapy; in contrast, psychotherapy alone cannot be expected to affect the organic process underlying the hypothyroidism. 3) In the patient who is hypothyroid and likewise having domestic difficulties, it is frequently rewarding to investigate the other partner for thyroid-metabolic deficiency.

Summary and Conclusions. 1) In the process of investigating 123 cases of proven hypothyroidism, a significant and what is believed to be previously unreported incidence (26%) of thyroid deficiency occurring in 2 or more members of the same family group, usually husband and wife, was encountered.

2) It is suggested that whenever a case of hypothyroidism is diagnosed in a patient, the thyroid status of all available members of that individual's family be investigated. For this purpose the Lawson kinemometer has proved to be well-suited for screening large numbers of patients for the presence of thyroid-metabolic hypofunction. In patients showing a borderline or prolonged reflex time on the kinemometer, the PBI before and after TSH is recommended as an accurate test to establish or disprove the existence of thyroid deficiency.

3) Whether the common occurrence of hypothyroidism among members of a family or in the population at large is due to a viral thyroiditis setting into play an auto-immune response to released thyroglobulin or other thyroid antigens and eventual thyroid failure, though an attractive hypothesis to explain the present findings, is still to be proven. Four of 15 couples report a bout of mumps in one or both members shortly before the onset of their hypothyroid symptoms.

4) When hypothyroidism is diagnosed in one member of a married couple, it is especially important to investigate thyroid function in the other partner in cases of infertility or marital discord.

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SUMMARIO IN INTERLINGUA

Incidentia de Hypothyroidismo in Plus que Un Membro de Un Familia

1. In le processo del investigation de 123 casos de provate hypothyroidismo un significative incidentia de deficientia thyroide in plus que un membro del mesme familia esseva incontrate. Iste incidentia amontava a 26%. Usualmente marito e marita esseva implicate. Il pare que le phenomeno ha non previemente essite reportate.

2. Es recommendate que quandocunque un caso de hypothyroidismo es diagnosticate in un patiente, le stato thyroide de omne accessibile membros de su familia es investigate. Pro iste objectivo le cinemometro de Lawson se ha provate multo utile, proque illo permitte le triation de grande numeros de patientes pro le presentia de hypofunction thyroido-metabolic. In patientes in qui le tempore de reflexo monstrate per le cinemometro es marginal o prolongate, determinationes de iodo ligate a proteina ante e post administrationes de hormon thyroido-stimulante es recommendate como un accurate test pro provar le presentia o le absentia de deficientia thyroide.

3. Il es possibile que le occurrentia commun de hypothyroidismo in membros del mesme familia (o in le population in general) es le effecto de un thyroiditis virusal que precipita un responsa auto-immun al liberate thyroglobulina o a un altere antigeno thyroide con le resultato, in le curso del tempore, de disfallimento thyroide. Pro explicar le constatationes del presente studio, le mentionate hypothese es multo attractive, sed illo remane a provar. Quatro del 15 pares de maritatos reporta un episodio de parotiditis in un o ambe membros brevemente ante le declaration de lor symptomas hypothyroide.

4 .Quando hypothyroidismo es diagnosticate in un membro de un par de maritatos, il es specialmente importante investigar le function thyroide in le altere in casos de infertilitate o de discordo marital.

EFFECT OF DIURETICS UPON THE SERUM PROTEIN BOUND IODINE AND THE THYROIDAL UPTAKE OF RADIOACTIVE IODINE

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Spuriously low serum protein-bound iodine (PBI) values were noted to follow the injection of mercurials in patients by Meyers and Man[7] in 1951. Using the distillation technique of Kydd, Man and Peters[6], they reported that iodide was precipitated by mercury during the process of digestion and therefore failed to distil over. Since then clinicians have questioned the significance of low serum PBI determinations, if the patients had received mercurial injections.

However, in 1951, Barker[1] introduced the alkaline-ash method for PBI determination, in which both the digestion and the distillation steps were eliminated. We wondered if, using this technique, the serum PBI determinations would be unaffected by mercurial injections. The only available information concerning this was Bondy's observations[3] that mercury does not interfere with the alkaline dry ash method. In the present study, determinations of serum PBI were made prior to, and at intervals after, the injection of meralluride.

Since diuretics do cause increased excretion of chlorides, studies were made to determine if they also increase ioduresis and perhaps thus result in a lower thyroidal accumulation of I_{131}. Finally, we sought to determine the effects of other potent diuretics, such as hydrochlorothiazide and acetazolamide (Diamox) upon ioduresis, 24-hour thyroidal uptake of I_{131} and serum PBI.

Material and Methods. Hospitalized patients, some of whom were in congestive heart failure, were the subjects of these studies. They were all clinically euthyroid and had not received either iodide or any medication which is known to interfere with the tests employed.

Each of the patients received one of the following diuretics: a single intramuscular injection of 2 ml. of meralluride (Mercuhydrin), or two 50 mg. tablets of hydrochlorothiazide orally at a 12-hour interval, or four 250 mg. tablets of acetazolamide at 6-hour intervals. Blood was drawn prior to, and 4, 24, and 48 hours after, the mercurial injection. In the experiments, in which the oral diuretics were administered, blood was drawn prior to, and 24 and 48 hours after, the ingestion of the first tablet. The protein-bound iodine determinations on all sera from a given patient were run on the same day, to eliminate day to day variation in the method. The serum PBI was determined by the alkaline dry-ashing method of Barker[1].

A tracer dose of approximately 5 microcuries of I_{131} was administered orally prior to breakfast to determine both the control

value for the 24-hour thyroidal uptake and the amount of urinary excretion of I_{131} for each of 3 consecutive days. These studies were repeated after either the injection of the meralluride or the ingestion of the first diuretic tablet. Prior to the administration of the second tracer dose of I_{131}, the residual radioactive iodine from the initial tracer dose in the thyroid gland was determined. The second tracer dose was then calculated to contain about ten times as much radioactivity as the observed residual. Control studies, in which no diuretics were administered, demonstrated that the first and second 24-hour uptake, calculated in the manner indicated above, were essentially the same.

The initial 24-hour urinary excretion of I_{131} was compared with that immediately following the administration of the diuretic. The radioactivity excreted in the second and third days of the control period was measured to determine whether significant amounts of radioactivity from the first dose were being excreted at the time the second dose of I_{131} was given. No significant radioactivity was found in the urine on the third day after ingestion of the initial tracer dose.

Urinary creatinine excretions were determined to establish the completeness of the 24-hour urinary collections. Urinary volumes and urinary excretions of chlorides were measured to determine the effectiveness of meralluride or acetazolamide. After the administration of the hydrochlorothiazide, the urinary excretion of sodium and potassium were also determined.

TABLE 1.—EFFECT OF DIURETICS UPON THE SERUM PBI LEVELS

Patients	*Control* μg./100 ml.	*4 Hr.* μg./100 ml.	*24 Hr.* μg./100 ml.	*48 Hr.* μg./100 ml.
(a) *Meralluride*				
V.G.	5.7	5.4	6.7	6.4
M.R.	6.6	6.0	6.3	6.2
D.M.	5.2	5.1	5.4	4.9
R.B.	6.2	5.9	—	6.4
C.S.	6.7	6.5	6.5	7.7
I.S.	5.3	5.4	6.4	—
V.D.R.	6.4	5.5	5.5	5.1
C.S.	4.5	4.9	—	6.5
C	5.3	3.8	4.9	5.8
B.R.	3.9	4.9	4.3	4.4
J.S.	5.3	4.0	5.9	4.3
B.	5.4	5.6	5.1	6.0
Mean	5.5	5.2	5.7	5.8
(b) *Hydrochlorothiazide*				
Mc	5.3	—	6.0	6.0
L.H.	4.1	—	4.3	4.3
A.B.	5.3	—	6.4	5.2
Mean	4.9	—	5.5	5.1
(c) *Acetazolamide*				
M.	6.9	—	6.7	6.0
Mc	3.9	—	4.0	4.1
V.	6.2	—	6.3	6.0
Mean	5.6	—	5.3	5.3

Results. EFFECT OF DIURETICS UPON SERUM PBI LEVELS. Twelve patients received an injection of meralluride. The data in Table 1a reveal that there was no significant change in the level of serum PBI in these patients, at either 4, 24, or 48 hours after the administration of the mercurial. The mean serum PBI values after the injection, differed from the mean control PBI by no more than 0.3 μg. per 100 ml.

Three patients were given 100 mg. of hydrochlorothiazide and 3 other patients received 1000 mg. of acetazolamide. The data in Tables 1 b and c reveal that there was no significant change in levels of PBI at either 24 or 48 hours after the first dose was ingested.

TABLE 2.—EFFECT OF DIURETICS UPON THYROIDAL UPTAKE AND URINARY EXCRETION OF I_{131}

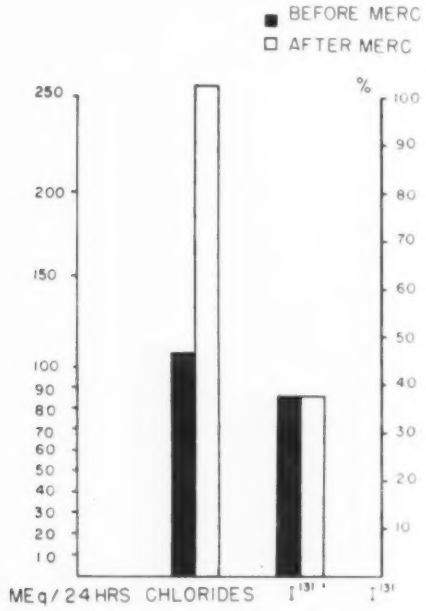
	Uptake		*Urinary Excretion*	
Patients	*Before* %	*After* %	*Before* %	*After* %
(a) *Meralluride*				
J.S.	30	41		
B.R.	33	35		
D.R.	37	38	28	39
I.S.	46	46	32	34
C.S.	24	22	38	29
R.B.	29	29	48	40
D.M.	41	28	31	43
M.R.	40	37	28	35
H.L.	47	62	51	39
Mean ± SEM	36±2.6	37±3.9	37±3.6	37±1.7
(b) *Hydrochlorazide*				
H.E.	31	26	42	33
V.P.	24	22	38	42
M.B.	30	30	55	51
O.E.	32	30	63	65
I.M.	32	23	69	73
A.C.	20	16	32	28
C.F.	37	32	21	28
C.D.	29	23	35	36
S.M.	13	14	57	84
M.	28	39	42	68
D.F.			42	44
Mean ± SEM	27.6±2.2	25.5±2.2	45±4.3	50±5.8
(c) *Acetazolamide*				
M.M.	28	36	24	38
J.P.	33	26	41	46
M.L.	30	31	42.5	30
J.P.	34	24	42	47
Mean	31	29	37.3	40

EFFECT OF DIURETICS UPON THYROIDAL UPTAKE AND URINARY EXCRETION OF I_{131}. a) *Meralluride.* Nine patients, 6 of whom were in congestive heart failure, received meralluride. The data in Table 2a reveal that there was no significant change in either the thyroidal uptake of I_{131} or the urinary excretion of this radioisotope, as the result of mercurial administration. However, the drug produced marked excretion of chlorides as seen in Fig. 1, especially in those patients with edema.

b) *Hydrochlorothiazide.* Eleven patients, 3 of whom were in congestive heart failure, received 100 mg. of hydrochlorothiazide orally. The data in Table 2b reveal that this diuretic agent

caused no significant change in either the thyroidal uptake or ioduresis. In 2 of the 9 studies there was a slight increase in ioduresis. However, the excretion of chlorides, sodium and potassium was markedly increased, as noted in Fig. 2.

dropped from 4 to 8 μg. per 100 ml. and that this effect persisted for as long as 48 hours. In their studies, the serum PBI was determined by means of distillation methods of Kydd, Man and Peters[6]. They concluded that the mercury combined with the iodide and



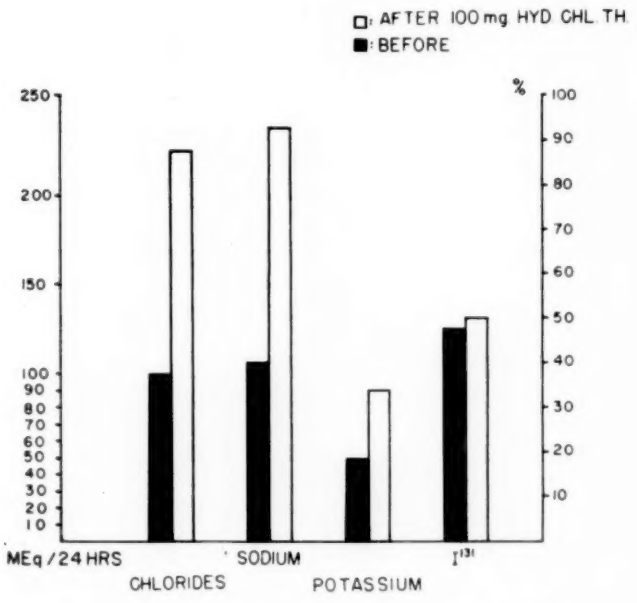
COMPARATIVE EFFECT OF MERCURIALS UPON URINARY EXCRETION OF CHLORIDES AND I^{131}

Fig. 1

3) *Azetazolamide.* Four patients, 3 of whom were in congestive heart failure, received 1000 mg. of acetazolamide. The data in Table 2c reveal that there was no significant change in either the thyroidal uptake of I_{131} or its urinary excretion. Three of these 4 patients showed a water diuresis unaccompanied by chloruresis as noted in Fig. 3.

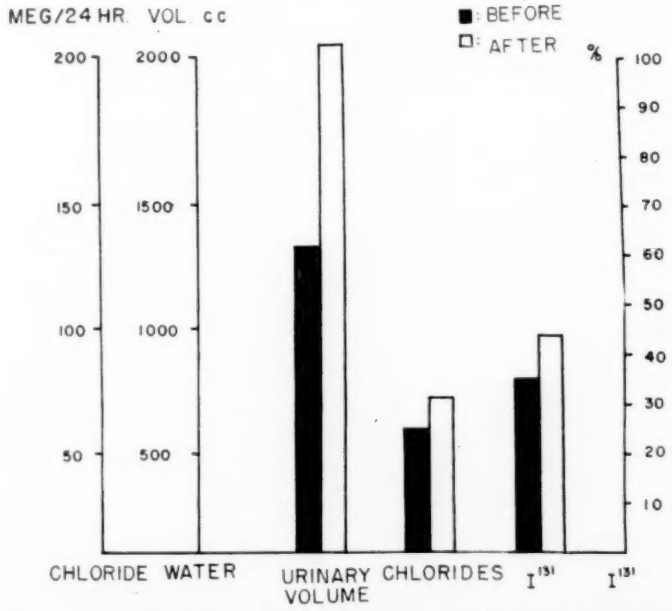
Discussion. Meyers and Man[7] reported that after the injection of mercurials, the level of the serum PBI prevented the distillation of the halide. Mercury as well as silver, fluoride or cyanide may directly interfere with the cerium-arsenic-iodine reaction by reducing the concentration of iodide ion, even when techniques other than the distillation is used (Zak *et al.*[8]).

However, we have been able to confirm Bondy's unpublished data[3] that parenterally administered mercury will not interfere with the alkaline-ashing procedures. This is probably due to the volatilization of the mercury at the



COMPARATIVE EFFECT OF HYDROCHLOROTHIAZIDE UPON URINARY EXCRETION OF CHLORIDES, SODIUM, POTASSIUM AND I^{131}

Fig. 2



COMPARATIVE EFFECT OF DIAMOX UPON URINARY EXCRETION OF WATER, CHLORIDES AND I^{131}

Fig. 3

temperature of 565° C., whereas the iodine, in the form of iodide, is not volatilized.

When a tracer dose of I_{131} is ingested, two organs compete for its collection from the blood: the thyroid gland, which traps and converts it into organic compounds, and the kidneys, which excrete it. Variations in the renal ability to excrete iodide usually do not significantly alter the 24-hour thyroidal uptake of I_{131}. Theoretically, however, one would expect that decreased renal ability to excrete iodide might result in high thyroid uptake of I_{131} and conversely that excessive renal excretion of iodide might result in decreased thyroidal accumulation of iodide.

The glomerular filtration of iodide can be influenced by thyroid activity (Hlad[5]), the status of the peripheral circulation, or by the direct effect of theophylline-ethylenediamine (aminophylline) on the glomerular blood flow (Bricker and Hlad[4]). Berson and Yalow[2] postulated that iodide and chloride ions are handled similarly at the renal tubular level. In cases of marked chloruresis, as found in Cushing's syndrome or induced by the administration of cortisone, the renal clearance of iodide was found to be increased. Bricker and Hlad[4] reported that neither sodium thiocyanate nor mercurials altered the renal tubular reabsorption of iodide but that para-aminohippurate loading did decrease tubular reabsorption of this halide. Our studies agree with the findings of Bricker and Hlad, in that the diuretics which we administered failed to increase the ioduresis even when they did initiate both chloruresis and water diuresis. We concur with their conclusion that the renal clearance of iodide is essentially independent of the renal clearance of either chloride, sodium, or potassium.

Summary. The acute effects of mercurial diuretics, hydrochlorothiazide and acetazolamide upon the serum PBI levels, 24-hour thyroidal uptake and 24-hour urinary excretion of I_{131} were studied in a group of patients, some of whom were in congestive heart failure with secondary fluid retention.

There was no interference by mercurials upon the determination of serum PBI when Barker's dry-ashing technique was used: its levels remained unchanged at intervals from 4 to 48 hours after the intramuscular injection of meralluride. Neither hydrochlorothiazide nor acetazolamide produced any acute change of the serum PBI levels.

The administration of mercurials, hydrochlorothiazide or acetazolamide failed to increase ioduresis and had no effect upon the 24-hour thyroidal uptake of I_{131} in normal subjects and also in patients with congestive heart failure.

ACKNOWLEDGMENT: The authors are grateful to Miss Betty Pomerantz and Mrs. Selma Epstein for their help in preparing the manuscript and to Miss Frances B. Watts for preparing the figures. They also wish to thank Mr. Gerald Dobkin of the routine chemical laboratory for doing the urinary electrolyte determinations.

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SUMMARIO IN INTERLINGUA

Le Effecto de Diureticos Super le Iodo Ligate a Proteina in le Sero e Super le Acceptation de Iodo Radioactive per le Glandula Thyroide

Esseva studiate, in un gruppo de patientes (incluse plures in congestive disfallimento cardiac con retention secundari de liquido), le effectos acute de diureticos mercurial, hydrochlorothiazida, e acetazolamida super le nivellos de iodo ligate a proteina in le sero, le acceptation per le glandula thyroide de iodo radioactive in 24 horas, e le excretion urinari de ille isotopo in 24 horas.

Esseva constatate nulle interferentia del mercuriales in le determination de iodo ligate a proteina seral quando le technica de Barker esseva empleate. Le nivellos de iodo ligate a proteina in le sero remaneva sin alteration post intervallos de ab 4 usque a 48 horas post le injection intramuscular de merallurida. Ni hydrochlorothiazida ni acetazolamida produceva ulle acute alteration del nivellos seral de iodo ligate a proteina.

Le administration de mercuriales, hydrochlorothiazida, o acetazolamida non augmentava le iodurese e exerceva nulle effecto super le acceptation de iodo radioactive per le glandula thyroide in 24 horas in subjectos normal como etiam in patientes con congestive disfallimento cardiac.

SUMMARIO IN INTERLINGUA

(See page 601 for original article)

Un Exploration del Action Antihypertensive de Chlorothiazida

Chlorothiazida es unic como diuretico in tanto que illo causa un perdita marcate del kalium del corpore e reduce un elevate tension de sanguine. Esseva postulate que le capacitate del droga de reducer le tension de sanguine es possibilemente relationate a su effecto kaliuretic.

Un previemente non tractate patiente de 51 annos de etate con non complicate "hypertension essential" esseva studiate per medio del technica del balancia metabolic. Ille esseva tractate con chlorothiazida. Su tension de sanguine esseva reducite per le droga. Concomitantemente ille habeva un perdita de 110 mEq de kalium del corpore. Le restitution del perdita de kalium non afficeva le reducite tension sanguinee.

Mesurationes del function renal e del hemodynamica renal revelava un relentation del filtration glomerular durante le administration del droga. Le filtration retornava al nivello de controlo quando le perditas de kalium esseva restituite. Le fluxo de plasma renal e le massa de excretion tubular remaneva normal perdurativemente. Le resistentias arteriolar afferente e efferente renal se reduceva durante que le droga esseva administrate, sed illos non remontava quando le kalium esseva restituite. Le relation inter le reduction del resistentia reno-arterial e le mechanismo primari del effecto de chlorothiazida non pote esser demonstrate, sed illo non es un function del reducite kalium del corpore.

STUDIES ON GROWTH HORMONE VII. THE ACTIVITY OF GROWTH HORMONE IN SUPPRESSION OF CORTISONE-INDUCED CLEFT PALATE AND FETAL ABSORPTION IN MICE

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There has been an increased interest in the occurrence of congenital cleft palate since Fraser and Fainstat[1,2] reported the positive effect of cortisone injection on its experimental production in mice. Kalter and Fraser[4] have since induced cleft palate in other mammals by similar means. Strean and Peer[9], on the basis of questionnaires distributed to their patients, concluded that for 232 documented cases, stress, during the first trimester of pregnancy, was an etiological factor in the occurrence of cleft palate. Ingalls and Curley[3] have drawn attention to hypoxia, as well as cortisone, as an etiological factor; and Strean also reported that the incidence of experimental cortisone-induced cleft palate in mice was reduced by diets containing an excess of "anticatabolic vitamins" (B_6, B_{12}, C, and so forth).

The work here reported† is based on the suggestion that some specific hormone may be able to act as a steroid antagonist during pregnancy, and hence prevent an increase in the incidence of cleft palate and that of fetal absorption both of which are seen in mice under cortisone treatment (Nishihara[5]).

Recently, Prudden, Pearson and Soroff[7] reported that growth hormone, under certain circumstances, accelerates metabolic recovery in the postoperative patient. Experimental studies in this laboratory (Prudden, Nishihara and Ocampo[6]) have also demonstrated a marked weight increase in postoperative rats treated with growth hormone as compared with postoperative control animals which showed either less gain or actual loss of weight. These postoperative studies clearly show that a modified response to the stress of operative trauma occurs in the presence of growth hormone, and, therefore, suggest that growth hormone may act as a steroid antagonist. This hypothesis has been tested by injection of growth hormone and cortisone simultaneously in mice as described below.

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and has been controlled by injection of certain other hormones with cortisone.

Materials and Methods. Virgin female mice of the Webster-Swiss strain, weighing approximately 25 gm., were used in all cases except for those multiparous females, of the same strain, which were compared with the primipara in the cortisone series. The mice were housed and fed in this laboratory for more than 2 weeks after shipment and experimentation was started only after they had reached the indicated weight. Food consisted of the Rockland mouse diet in pellet form.*

Three control groups, observed at different times, were studied: Groups A and B (these constitute an experimental group described elsewhere) (Nishihara[5]) which received no injections, and Group C which received injections of normal saline similar in volume to the hormone injections used for the treated animals.

The cortisone effect was studied with 2 groups of primipara observed at different times, Groups D and E. Group F, consisting of multipara, was also studied for a cortisone effect. The multiparous mice had all been bred, mated, and delivered in this laboratory to assure their multiparity. Cortisone was given by subcutaneous injection to all pregnant animals in these groups on the 12th through 15th days of gestation as cortisone acetate solution (concentration, 25 mg. per ml.) in a dose of 2.5 mg. (0.1 ml.).

For the growth hormone† series, 4 groups were employed:

Group G: Growth hormone injections were given simultaneously with cortisone. Cortisone dosage was as described above for Groups D, E, and F; growth hormone was given in a daily dosage of 0.2 mg. (concentration 2 mg. per ml. normal saline) for 4 consecutive days (12th through 15th days of gestation).

Group H: Growth hormone injections were given to this group starting one day earlier (11th day of gestation) than the cortisone injections and continued for 4 consecutive days. All dosages were the same as for Group G.

Group I: Growth hormone injections were started 2 days earlier (10th day of gestation) than cortisone injections and continued for 4 consecutive days. All dosages were the same as for Group G.

Group J: Growth hormone injections were given simultaneously with cortisone (12th through 15th days of gestation), but growth hormone dosage was increased to 0.6 gm. (0.3 ml.) per day. Cortisone dosage was the same as for Group G.

Progesterone and chorionic gonadotropin studies were also carried out as follows:

Group K: 1 mg. of progesterone (concentration 10 mg. per ml. in sesame oil) was injected for 4 consecutive days simultaneously with cortisone. Cortisone dosage was as described above.

Group L.: 125 international units of chorionic gonadotropin (concentration: 1000 international units per ml.) were injected for 4 consecutive days simultaneously with cortisone. Cortisone dosage was as described above.

The day of appearance of a vaginal copulation plug was counted as the first day of gestation. Those mice with vaginal plugs were then separated from the remainder of their respective groups, and of these, the bonafide pregnancies were diagnosed by palpation on the 11th day of gestation.

As in Fraser's series, the 12th through 15th days of gestation were chosen for injections, except where noted above for the growth hormone series. The injections were given between 10:00 a.m. and 11:00 a.m. A 22 gauge needle was inserted subcutaneously, extending from the median part of the back to one side of the lateral breast region. Cortisone was injected on one side; the test hormone was injected on the opposite side. In this way, mixing of the materials given and leakage were minimized. Maternal cannibalism was prevented by sectioning all pregnant mice on the 18th day of gestation.

Results. A. CONTROL STUDIES. The 3 control groups were studied over a period of several months. In Group A, observations were made on the number of offspring that were normal and those born with cleft palate. Observation of the number of fetal absorptions was omitted. In Group B, the offspring were classified according to whether they were normal, had cleft palate, or had undergone placental absorption. In Group C, these 3 classifications were

*Purchased from Rockland Farms, Rockland, New York.

†The growth hormone for this study was obtained as a gift from the Endocrinology Study Section of the National Institutes of Health.

applied to the offspring of controls which had been given saline injections, comparable in volume to the cortisone and growth hormone injections. Since the 3 groups constitute a repeated study, at different times, of essentially similar control animals, it is of interest to compare them with each other.

When Groups A and B are compared as to percentage of offspring which are normal and which have cleft palate, respectively (see Table 1), the differences by chi-square test are nonsignificant ($0.3>p>0.2$).

Groups B and C permit not only the comparison of incidence of normal and cleft palate offspring, but also the incidence of fetal absorption (see Table 2). The chi-square test shows nonsignificant differences between the 2 groups ($0.7>p>0.5$). In subsequent comparisons of controls with treated animals, Groups B and C will be combined and referred to as the combined control group.

TABLE 1.—CONTROL STUDIES ON INCIDENCE OF CLEFT PALATE IN PRIMIPAROUS MICE

Group	*Number of Normal Offspring*	*Number of Offspring with Cleft Palate*	*Total*
A	94	1	95
B	115	0	115

It seems clear that repeated studies on controls produced results which were essentially the same for each replication. This finding contrasts with the results obtained with the repeated cortisone studies (see below).

It has been reported (Ingalls and Curley[3]) that the incidence of cleft palate in normal control animals is 0.2%. Among control groups A, B, and C, considering only normals and cleft palate offspring, an incidence of 1:323 cleft palate has been observed. This is consistent (chi square test) with the expected incidence of 0.2%.

TABLE 2.—CONTROL STUDIES ON INCIDENCE OF FETAL ABSORPTION AND CLEFT PALATE IN PRIMIPAROUS MICE

Group	*Number of Normal Offspring*	*Number of Offspring with Cleft Palate*	*Number of Fetal Absorptions*	*Total*
B	115	0	11	126
C	113	0	7	120
B + C (Combined Control Group)	228	0	18	246

B. CORTISONE STUDIES. All of the control studies and most of the cortisone studies were carried out on primipara mice. Groups D and E were observed, several weeks apart, after treatment with cortisone. Conditions of injection and observation were made as uniform as possible; incidence of abnormalities for the 2 groups is shown in Table 3. When either Group D or Group E of the cortisone series is compared separately with the combined control group, or when the combined cortisone series is compared with the combined control group, the cortisone treated animals show a highly significant in-

TABLE 3.—CORTISONE STUDIES ON PRIMIPAROUS MICE

Group	*Number of Normal Offspring*	*Number of Offspring with Cleft Palate*	*Number of Fetal Absorptions*	*Total*
D	0	40	12	52
E	5	62	46	113
D + E (Combined Cortisone Group)	5	102	58	165

crease in the incidence of abnormal offspring. A series of multipara mice treated with cortisone also shows increased incidence of abnormal offspring when compared with the controls (Table 4). These results were anticipated from previous reports (Fraser and Fainstat[1], Fraser *et al.*[2], Ingalls and Curley[3], Nishihara[5]).

TABLE 4.—CORTISONE STUDIES ON MULTIPAROUS MICE

Group	*Number of Normal Offspring*	*Number of Offspring with Cleft Palate*	*Number of Fetal Absorptions*	*Total*
F	5	102	53	160

The differences between cortisone groups D and E, by way of contrast, were unanticipated but decidedly significant (chi square test: $0.02>p>0.01$). Hence, while the injection of cortisone produces an increase in the incidence of abnormalities among the offspring of primipara mice, the degree to which the incidence is increased varies significantly with the group of mice studied. This contrasts with the homogeneity exhibited by the several control groups (Table 1). Thus cortisone produces the effect of paradox by consistent influence to abnormal offspring and inconsistent production of percentage response. It seems reasonable to assume that cortisone, by sensitizing the pregnant animal to uncontrolled, small changes in laboratory conditions, for example, humidity, temperature, and so forth, is responsible for this effect.

When the 2 groups of primipara mice treated with cortisone are combined and compared with the series of multipara mice treated with cortisone (Tables 3, 4, and 5) the multipara show a small but highly significant trend to increased numbers of *normal* offspring (chi square test: $p<0.001$). This finding is in agreement with the observations of Strean and Peer[9] on the incidence of cleft palate in the human after the first born (see **Discussion** below). While the absolute magnitude of the difference between multipara and primipara mice is in doubt, due to the non-homogeneity of the cortisone groups, the resistance of the multipara to cortisone would seem to be clearly established.

C. GROWTH HORMONE STUDIES. Groups G, H, I, and J were simultaneously injected with growth hormone and cortisone. Table 6 summarizes the overall comparison between these animals and the control and combined cortisone groups, respectively. The differences in each case are highly significant ($p<0.001$). By converting these results to percentages (Table 7), it is observed that the growth hormone exerts little, if any, protective effect upon the incidence of cleft palate; however, it does markedly reduce the incidence of fetal absorptions, the reduced incidence adding to the percentage of normal offspring.

TABLE 5.—COMPARISON OF OFFSPRING FROM PRIMIPAROUS AND MULTIPAROUS MICE UNDER TREATMENT WITH CORTISONE

Group	*% Normal Offspring*	*% Offspring with Cleft Palate*	*% Fetal Absorptions*
D+E (Combined Primiparous Group)	3.0	61.8	35.2
F	15.0	42.4	42.4

Among the individual studies with growth hormone, Groups G, H, and I (Table 8) do not differ significantly from each other; it will be recalled

that these 3 studies are identical with respect to dosage of the hormones administered and differ only by the time administration of growth hormone was begun. However, Group J, representing a study with increased dosage of growth hormone, does differ significantly ($p<0.001$) from the other growth hormone groups, and furthermore, in the direction of increased incidence of fetal absorptions. It would appear that an optimum dosage exists for the protective effect exerted by growth hormone. It may be worthwhile in future studies to pursue this question with more complete gradation of dosages.

TABLE 6.—COMPARISON OF OFFSPRING FROM GROWTH-HORMONE AND CORTISONE TREATED PRIMIPAROUS MICE WITH OFFSPRING FROM CORTISONE TREATED PRIMIPAROUS MICE

Group	*Number of Normal Offspring*	*Number of Offspring with Cleft Palate*	*Number of Fetal Absorptions*	*Total*
Combined Control Group (B+C	228	0	18	246
Combined Cortisone Group (D+E)	5	102	58	165
Combined Growth Hormone Group (G+H+I+J)	47	160	64	271

TABLE 7.—COMPARISON, BY PERCENTAGES, OF OFFSPRING FROM GROWTH-HORMONE AND CORTISONE TREATED PRIMIPAROUS MICE WITH OFFSPRING FROM CORTISONE TREATED PRIMIPAROUS MICE

Group	*% Normal Offspring*	*% Offspring with Cleft Palate*	*% Fetal Absorptions*
Combined Control Group (B+C)	92.7	0.0	7.3
Combined Cortisone Group (D+E)	3.0	61.8	35.2
Combined Growth Hormone Group (G+H+I+J)	17.3	59.0	23.6

D. CORTISONE AND CHORIONIC GONADOTROPIN; CORTISONE AND PROGESTERONE. Groups K and L essentially controlled the effect of cortisone and growth hormone by testing the effect of cortisone with chorionic gonadotropin and progesterone, respectively. The results are shown in Table 9. Differences between Groups K and L and cortisone-treated animals or cortisone-growth hormone treated animals are readily apparent, and are highly significant ($p<0.001$). A striking finding in both cases is the shift of offspring into a single category, that is, placental absorption. It is important to note that these hormones show directional effects almost diametrically opposed to that of growth hormone.

Discussion. These data demonstrate that parenteral growth hormone administered to pregnant mice has preventive effects on cortisone-induced fetal absorptions; consequently more normal offspring and fewer placental absorptions are observed for the growth-hormone treated mice. However, no significant protective effect by growth hormone on cleft palate formation was observed.

Of some interest too is the finding that multiparous mice were more resistant to the cortisone effect than primiparous mice. This is suggestive in view of Strean's and Peer's[9] finding of much reduced incidence of cleft palate among the second children of families with

first-born cleft palate histories. The mechanism responsible for the increased resistance of multipara is not known, but is possibly related to the greater stress imposed on the individual by a first pregnancy in comparison to subsequent ones.

be speculated upon inasmuch as the cortisone response itself is not adequately explained. Further study on the mechanisms seems indicated.

It is clear in any case that a specific effect by growth hormone is involved since the gonadotropin and progester-

TABLE 8.—COMPARISON OF OFFSPRING FROM PRIMIPAROUS MICE TREATED WITH GROWTH HORMONE AND CORTISONE UNDER VARIOUS TEATMENT SCHEDULES

Group	*Total Number of Offspring*	*% Normal Offspring*	*% Offspring with Cleft Palate*	*% Fetal Absorptions*
G(Growth Hormone Simultaneously with Cortisone)	56	23.2	66.1	10.7
H(Growth Hormone Started 1 day Before Cortisone)	42	23.8	57.1	19.0
I(Growth Hormone Started 2 days Before Cortisone)	87	16.1	58.6	25.3
J(Increased Dosage of Growth Hormone)	86	11.6	55.8	32.6

TABLE 9.—COMPARISON OF OFFSPRING FROM PRIMIPAROUS MICE TREATED WITH PROGESTERONE OF CHORIONIC GONADOTROPIN AND CORTISONE WITH PRIMIPAROUS MICE TREATED WITH CORTISONE

Group	*Total Number of Offspring*	*% Normal Offspring*	*% Offspring with Cleft Palate*	*% Fetal Absorptions*
Combined Control Group (B+C)	246	92.7	0.0	7.3
Combined Cortisone Group (D+E)	165	3.0	61.8	35.2
Progesterone and Cortisone Group (K)	57	0.0	0.0	100.0
Chorionic Gonadotropin and Cortisone Group (L)	50	0.0	0.0	100.0

The shift with growth hormone administration from placental absorption to more normal offspring may be attributed to an increased resistance to cortisone evoked by the growth hormone, or an increased acceleration of the development of the fetuses, or possibly a chemical antagonism between the two hormones. The protective action of growth hormone can thus only

one controls were not only opposite in trend to the growth hormone results, but apparently acted to reinforce the trend to fetal absorption so that no offspring were viable at the end of the gestation period. Sobel[8] has also concluded that growth hormone is a cortisone antagonist and acts to protect the chick embryo against cortisone induced congenital anomalies.

Summary. Cortisone was administered to pregnant mice, primipara and multipara. Parenteral growth hormone, chorionic gonadotropin, and progesterone were administered in conjunction with cortisone to pregnant primipara mice. The following results were obtained:

1. Multipara were significantly more resistant to the production of cleft palate by cortisone than were primipara.

2. Growth hormone counteracted the effect of cortisone to a significant extent: more normal offspring and correspondingly fewer placental absorptions were observed. The incidence of cleft palate with growth hormone protection, however, remained virtually unchanged from that found in mice treated only with cortisone.

3. Parenteral progesterone and chorionic gonadotropin administered simultaneously with cortisone terminated pregnancy in every case.

It is concluded that growth hormone in pregnant mice exerts a specific protective effect against cortisone, permitting significantly more viable offspring to be produced at the end of the period of gestation.

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SUMMARIO IN INTERLINGUA

Studios Relative al Hormon de Crescentia
VII. Le Activitate de Hormon de Crescentia in le Suppression del Palatoschisis e del Absorption Fetal Stimulate in Muses per le Injection de Cortisona

Cortisona esseva administrate a muses pregnante, primiparas e multiparas. Hormon de crescentia, gonadotropina chorionic, e progesterona esseva administrate parenteralmente in conjunction con cortisona a primipare muses pregnante. Le sequente resultatos esseva observate:

1. Multiparas esseva significativemente plus resistente al production de palatoschisis per cortisona que primiparas.

2. Hormon de crescentia contrariava le effecto de cortisona a grados significative. Esseva observate un prole plus normal e un correspondente reduction del absorptiones placental. Tamen, le incidentia de palatoschisis remaneva virtualmente sin alteration in despecto del protection con hormon de crescentia.

3. Progesterona e gonadotropina chorionic administrate parenteralmente insimul con cortisona terminava le pregnantia in omne caso.

Es concludite que hormon de crescentia in muses pregnante exerce un specific effecto protectori contra cortisona, permittente le production de significativemente plus numerose juvenes viabile al fin del periodo de gestation.

THE SYNDROME OF POLYCYSTIC OVARIES AND HYPERTHECOSIS A CLINICAL EVALUATION*

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Stein and Leventhal[21] in 1935 described a syndrome consisting of menstrual irregularities, sterility, obesity and hirsutism with bilaterally enlarged polycystic ovaries. Since then, numerous reports have confirmed their observations. In 1939, Stein and Cohen[20] reported that bilateral ovarian wedge resection produced normal menstrual periods in most patients and that some of them even became pregnant following operation. On the other hand, there has been a certain amount of confusion in defining exactly what is the Stein-Leventhal syndrome both from the clinical and the pathological point of view. There has been a tendency to make separate entities of similar clinical syndromes in which the ovaries are not greatly enlarged but present an almost identical histological picture. Clinicians have often hesitated a long time before agreeing to an exploratory laparotomy in patients with unexplained menstrual irregularities and sterility if they did not have the complete clinical picture described above, especially if the ovaries were not definitely large either by palpation or gynecography. Many pathologists have been reluctant to confirm such a diagnosis if they did not find all the elements of the classical pathological picture. Furthermore, the etiology and pathogenesis of the Stein-Leventhal syndrome have always been, and still are, fairly obscure.

For the above reasons, it was decided to study clinically and pathologically the findings in 18 patients with the Stein-Leventhal syndrome and to explore biochemically the possibility of a primary ovarian or adrenocortical dysfunction in this syndrome.

Subjects and Methods. Our patients were 18 young women with the syndrome of polycystic ovaries and hyperthecosis seen in the last 2 years, in which the diagnosis was confirmed by the macroscopic appearance of the ovaries at laparotomy and by histological study of the ovarian tissue obtained from a bilateral wedge resection. Histological sections of ovarian tissue were all prepared by the same technique and examined by the same pathologist (S.L.).

The total urinary 17-ketosteroids were measured using the technique of Drekter *et al.*[4] with addition of the chloroform extraction of the Zimmerman chromogens recommended by Cahen and Salter[3]. The procedure of Reddy[18] was used to determine the total urinary 17-hydroxycorticosteroids. The bioassay of urinary follicle stimulating hormone

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Acton X, utilized for the ACTH tests, was kindly supplied by Nordic Biochemicals, Montreal, Canada.

(FSH) was performed after adsorption of the urinary gonadotrophins on kaolin as described by Bradbury, Brown and Brown[1]. In some patients, urinary estrogens were measured by the Allen-Doisy bioassay. In 8 patients, the urinary 17-ketosteroids were separated by column chromatography by the technique of Lanthier *et al.*[14].

Results. a) CLINICAL EVALUATION OF THE PATIENTS. (see Table 1). Our 18 patients had a mean age of 25 with a range of 20 to 39 when they were first seen at the Endocrinology Clinic. The mean age of the menarche was 14 years and it ranged from 11 to 20. Nine of the patients had a normal weight, 2 were slightly overweight and 7 were definitely obese. Hirsutism was barely noticeable in 3, slightly more apparent in 6 patients and much more pronounced in 7. Two patients were markedly hirsute. Seventeen of the women had a history of oligo-hypomenorrhea and 16 of them had periods of amenorrhea varying from 3 months to 13 years. Two patients presented themselves with meno-metrorrhagia; in one patient they had been present since the menarche while the other woman had oligo-hypomenorrhea and periods of amenorrhea for 20 years previously up to a year before presenting meno-metrorrhagia. Only 5 of the 18 patients had normal menstrual periods from 4 months to 14 years before presenting oligo-hypomenorrhea and periods of amenorrhea. Thirteen of our 18 women were married. Sterility had been present in all but one patient

TABLE 1.—CLINICAL FINDINGS

Patient	*Age*	*Weight*	*Hirsutism*	*Oligo-Hypo-menorrhea*	*Amenorrhea longest period*	*Meno-metror-rhagia*	*Normal menstrual periods*	*Sterility*
B.B.	34	N	××	Yes	3 Months	Yes	None	8 Years
A.B.	39	O	×××	Yes	13 Years	None	14 Years	14 Years
S.C.	31	N	×××	Yes	12 Months	None	None	9 Years
A.C.	25	O	×××	Yes	7 Months	None	None	4 Years
A.Co.	26	O	×	Yes	None	None	7 Years	No
S.D.	21	S.O.	××	Yes	7 Months	None	None	1 Year
T.D.	21	N	××	Yes	None	None	None	Single
L.E.	21	N	××××	Yes	10 Months	None	None	Single
C.G.	21	N	×	None	3 Months	Yes	4 Months	1 Year
N.L.	20	N	××	Yes	12 Months	None	None	Single
C.L.	24	S.O.	×××	Yes	5 Months	None	None	5 Years
B.L.	27	N	×	Yes	6 Months	None	None	5 Years
D.L.	29	N	×××	Yes	8 Months	None	None	Single
C.M.	21	O	××	Yes	8 Months	None	None	1 Year
J.P.	21	N	×××	Yes	10 Months	None	None	1 Year
M.R.	23	O	××	Yes	4 Months	None	None	Single
A.S.	29	O	×××	Yes	7 Months	None	7 Years	7 Years
P.T.	24	O	××××	Yes	5 Years	None	7 Years	6 Years

TABLE 2.—PATHOLOGICAL FINDINGS

Patient	*Ovarian Size*	*Fibrous Capsule*	*Microcysts*	*Theca Hypertrophy*	*Stroma Hyperplasia*	*Corpus Luteum*
B.B.	Slightly Englarged	×	×	0	0	0
A.B.	Large	×××	×××	××××	×××	0
S.C.	Large	××××	×	××××	×	0
A.C.	Large	×××	×××	×××	0	Yes (functional)
A.Co.	Slightly Enlarged	×××	××	××××	0	0
S.D.	Slightly Enlarged	××××	×××	××××	×	0
T.D.	Slightly Enlarged	××××	××	0	Fibrous	Yes (functional)
L.E.	Large	××××	××××	××××	Fibrous	Yes (old)
C.G.	Large	×××	××××	××××	×	0
N.L.	Slightly Enlarged	××××	××××	××××	0	0
C.L.	Large	0	×××	×××	0	0
B.L.	Slightly Enlarged	×××	×××	×××	Fibrous	0
D.L.	Slightly Enlarged	0	×××	0	0	Yes (functional)
C.M.	Slightly Enlarged	×××	××	××××	0	0
J.P.	Normal	××××	××××	××××	0	0
M.W.	Large	××××	××××	××××	×××	0
A.S.	Slightly Enlarged	×××	×××	0	×	0
P.T.	Large	××××	××××	××××	×	0

from one to 14 years. The other patient had had one normal pregnancy and delivery followed by 4 miscarriages.

b) OVARIAN PATHOLOGY (see Table 2). At laparotomy all ovaries had a pearly white (oyster-like) color. They were bilaterally enlarged in 17 cases, although only slightly in 9 patients in whom they were considered to be around the upper limit of normal. The ovaries were grossly enlarged in 8 cases.

The tunica albuginea was markedly thickened in 15 cases, slightly in one and of normal thickness in only 2 instances. Microcysts were present in all ovaries examined; they were very numerous in 13 patients and moderately in 5. Theca hypertrophy was noticeable in 14 patients and completely absent in only 4 instances. Definite hyperplasia of the ovarian stroma was present in only 2 patients; it was present to a very slight extent in 5 others.

Stroma hyperplasia was absent in 8 instances, while fibrosis of the ovarian stroma was present in 3 cases. A recent functional corpus luteum was noted in only 3 patients.

c) HORMONAL STUDIES (see Table 3). Twenty-seven determinations of the total urinary 17-ketosteroids were done in the 18 patients. The values found ranged from 3.1 to 25.0 mg. with a mean of 14.2 mg. per 24 hours. Values over 20 mg. were found in only 3 patients. Normal values for total urinary 17-ketosteroids in young women by this technique range from 5.0 to 15.0 mg. with a mean of 10.0 mg. per 24 hours.

Twenty-four determinations of the total urinary 17-hydroxycorticosteroids were made in 15 of the 18 patients. All the recorded values fell within normal limits except in one patient in whom a value slightly over the upper limit of normal was found one day, but was followed by a normal value the next day. Following 2 days of control urine collections, a standard 2-day intravenous ACTH test (Renold *et al.*[19]) was done in 9 patients. The increase in both the urinary 17-hydroxycorticosteroids and 17-ketosteroids was well within the range observed in normal women of comparable age during ACTH stimulation. Urinary FSH was

TABLE 3.—URINARY HORMONAL DETERMINATIONS

	Urinary 17-Ketosteroids mg. per 24 hr.				*Urinary 17-Hydroxycorticoids mg. per 24 hr.*				*Urinary F S H m.u. per 24 hr.*	*Urinary Estrogens m.u. per 24 hr.*
Patient	*Control*	*Control*	*ACTH*	*ACTH*	*Control*	*Control*	*ACTH*	*ACTH*		
E.B.	11.8				5.0				+52.8	
A.B.*	10.6 (25.0)	12.8	11.0	14.0	8.4	6.1	16.9	20.2	+105.6	+40.0
S.C.	11.2	10.4	13.3	16.5	3.9	4.7	22.6	27.0	+13.2	
A.C.	6.4	8.2			4.2	5.6			+13.2	
A.Co.	21.8								−6.6	+160
S.D.	16.6		18.2	23.7	9.7		13.9	15.8	−6.6	+160
T.D.	15.4	15.3	25.4	26.9	6.8	3.8	18.4	23.4	−6.6	
L.E.	11.7	15.7	24.4	27.7	6.4	8.4	29.2	33.8	+13.2	
C.G.	14.0								+13.2	+160
N.L.	10.2	11.3				5.1			+52.8	
C.L.	14.8	15.0	23.2	33.0	6.1	3.5	24.1	26.1	+13.2	+160
B.L.	13.4				7.0				+6.6	
D.L.	3.1					4.2			−6.6	
C.M.	16.2	9.8	15.7	17.4	6.6	6.9	12.7	14.9	+6.6	
J.P.	10.8				3.2				+52.8	
M.W.	21.4	24.3	36.3	46.0	6.3	6.8	26.5	36.5	+13.2	
A.S.	11.1	15.0	15.5	15.5	12.8	8.6	27.6	34.6	+52.8	
P.T.	13.5								−6.6	+80

*Values for F S H , Estrogens and 17-KS 25.0 mg. were found pre-operatively; all other values were found post-operatively.

normal in 12 patients, low in 5. Urinary estrogens were determined in only 6 cases and were found within the normal range in 5. One patient (A.B.) had low urinary estrogens and a slight increase in urinary FSH. This patient was 39 years old at the time of study and complained of hot flashes; she was probably starting her menopause.

The urinary 17-ketosteroids were separated on a silica gel column into 3 groups: androsterone + etiocholanolone, dehydroepiandrosterone and the 11-oxygenated 17-ketosteroids according to the technique of Lanthier *et al.*[14]. Three patients were found to have an increased excretion of androsterone + etiocholanolone, the mean value for those 3 patients was 10.6 ± 3.0 mg. per 24 hours (the mean value for 8 normal women was 4.5 ± 1.6 mg. per 24 hours); $P<0.001$. One patient excreted 5.8 mg. of dehydroepiandrosterone per 24 hours (the mean value for 8 normal women was 1.6 ± 1.0 mg. per 24 hours). The 4 other cases had a completely normal urinary 17-ketosteroid chromatographic pattern.

TABLE 4.—COURSE OF THE PATIENTS AFTER BILATERAL OVARIAN WEDGE RESECTION

Patient	*Months after Treatment*	*Menstrual periods*	*Pregnancies*	*Hirsutism*
B.B.	♀	N	0	No Change
A.B.	*			No Change
S.C.	15	N	1	No Change
A.C.	♀	N	0	No Change
A.Co.	♀7	N	0	No Change
S.D.	1♀	N	1	No Change
T.D.	10	N	Single	No Change
L.E.	6	N	Single	No Change
C.G.	4†			No Change
N.L.	1		Single	No Change
C.L.	19	N	0	No Change
C.L.	19	N	0	No Change
B.L.	16	N	1	No Change
D.L.	11	N	Single	No Change
C.M.	15	N	0	No Change
J.P.	15	None	0	No Change
M.R.	6	N	Single	No Change
A.S.	3	N	0	No Change
P.T.	♀4‡			

*Total hysterectomy and bilateral oophorectomy for reasons unknown.
†Total hysterectomy and bilateral oophorectomy for severe and intractable meno-metrorrhagia.
‡No follow up.

d) COURSE OF THE PATIENTS AFTER OVARIAN WEDGE RESECTION (see Table

4). A bilateral ovarian wedge resection was done in 16 of the 18 patients, some of whom have been followed up to 27 months postoperatively. A total hysterectomy with bilateral oophorectomy was done in the other 2 patients; in one case (C.G.), the radical operation was done for severe and intractable uterine bleeding, while in the other case (A.B.) it was done for unknown reasons in another hospital. In only one patient do we lack follow-up information because she never returned to our Clinic.

Out of the remaining 15 patients, one (J.P.), a married woman, is still amenorrheic 15 months after ovarian wedge resection. The 14 other patients have regular menstrual cycles and the daily temperature curve is suggestive of ovulation in the 4 cases in which it was obtained. Out of those same 14 patients, 9 are married and had been sterile from one to 9 years before ovarian wedge resection. Three of these patients have since become pregnant; one (B.L.) has delivered a normal full-term infant, another (S.C.) a diabetic, has had a miscarriage after 2½ months of pregnancy and the other patient (S.D.) is now 8½ months pregnant.

There has been absolutely no change in the hirsutism in any of these patients in the period of observation.

In 4 patients in which the urinary 17-ketosteroids were slightly elevated (14 to 25 mg. per 24 hours), a lower value (7.7 to 11.7 mg. per 24 hours) was recorded one to 4 months after bilateral ovarian wedge resection.

Discussion. The first fact emerging from the clinical review is the relative frequency of the polycystic ovaries and hyperthecosis syndrome. Eighteen patients were diagnosed as such within 2 years in a general hospital; a number of other patients with the same syndrome were not included in this series because of insufficient investigation. The following are some of the other facts standing out of the clinical review. Most of the patients were young, 10 of them being below the mean age of 25 years. Only half the patients in the series were definitely overweight. Hirsutism, although very difficult to evaluate, was present in all cases but certainly only of very minor degree in 3 of them. Thirteen of the 18 patients had menstrual irregularities dating back to the menarche. The most constant complaint was oligo-hypomenorrhea which was present in all patients except in one (C.G.) who presented with a history of menometrorrhagia since menarche. Only 2 patients did not have periods of amenorrhea. Out of the 13 married women, only one had had a normal pregnancy which was later followed by 4 miscarriages. The 12 other married women had been sterile from one to 14 years.

The ovaries were definitely large in 8 cases. They were only slightly enlarged in all the other patients except in one in which they were definitely of normal size. The histological findings were essentially those described by Stein and Leventhal in their original publication[21]. A functional corpus luteum, the witness of recent ovulation, was found in only 3 cases.

The clinical course of the patients after ovarian wedge resection was excellent, only one failing to respond with normal menstrual periods. We did not treat any of our patients with corticosteroids, although good results have been published by a number of investigators (Gold and Franck[7], Greenblatt *et al.*[8], Jones, Howard and Langford[12], Laffargue *et al.*[13], Perloff and Channick[15], Perloff *et al.*[16]). We preferred obtaining ovarian tissue for histological study and not to expose these young women to some of the pitfalls of prolonged corticosteroid therapy.

Determination of the urinary estro-

gens and FSH were of no diagnostic significance and did not point out any factor that might be important in the pathogenesis of the disease; this fact had already been pointed out by other workers (Ingersoll and McDermott[9], Laffargue *et al.*[13], Pesonen, Timmonen and Mikkonen[17]).

The values for the urinary 17-hydroxycorticosteroids were within normal limits during the control period and under ACTH stimulation. The only finding that may be of some significance was a mean value of 14.2 mg. per 24 hours for the urinary 17-ketosteroids which is 4.2 mg. over the mean for normal women, although only 3 patients had values of 20 mg. or more. This finding is in agreement with reports from many investigators (Buxton and Vande Wiele[2], Gallagher *et al.*[5], Gemzell, Tillinger and Westman[6], Ingersoll and McDermott[9], Jailer and Vande Wiele[10], Johnsen[11], Laffargue *et al.*[13], Perloff *et al.*[16], Pesonen, Timonen and Mikkonen[17]). The response of the urinary 17-ketosteroids to ACTH stimulation was within normal limits in all patients.

As Gemzell, Tillinger and Westman[6] stated, it is very difficult to find a correlation between hirsutism, ovarian pathology and the total urinary 17-ketosteroids.

We have selected from the medical literature 33 proven cases of the Stein-Leventhal syndrome in whom a chromatographic separation of the urinary 17-ketosteroids had been performed. Because of the variations in hydrolysis, separation and colorimetric procedures, the values are not readily comparable between themselves and with our own figures. Nonetheless, certain trends are apparent and are in agreement with our preliminary findings in 8 patients. Buxton and Vande Wiele[2] in 1954 reported a normal urinary 17-ketosteroid chromatographic pattern in 6 cases and an increased level of dehydroepiandrosterone in one patient. Also in 1954, Jailer and Vande Wiele[10] described a normal urinary 17-ketosteroid chromatographic pattern in 5 patients and an increased level of dehydroepiandrosterone in 4 other cases. Johnsen[11] in 1956 reported 5 cases of the Stein-Leventhal syndrome with abnormal patterns: 3 cases had an increased excretion of androsterone, 3 had an increased level of etiocholanolone and one patient had a high value for dehydroepiandrosterone. An increased level of androsterone and etiocholanolone with a slight increase in the 11-oxygenated 17-ketosteroids was reported by Gallagher *et al.*[5] in 1958. Eight cases were studied by Pesonen, Timonen and Mikkonen[17] in 1959; they found an increased excretion of androsterone and etiocholanolone in 5, of dehydroepiandrosterone in 4 and of the 11-oxygenated 17-ketosteroids in 2. In our 8 cases, 3 had an increased level of androsterone + etiocholanolone, one an increased level of dehydroepiandrosterone and the 4 others had a completely normal urinary 17-ketosteroid chromatographic pattern.

Summarizing the information obtained from the separation of the urinary 17-ketosteroids in patients with the Stein-Leventhal syndrome, it seems that some patients have an increased level of androsterone and etiocholanolone, others have an increased level of dehydroepiandrosterone, a few show a slightly increased 11-oxygenated 17-ketosteroid fraction, while still others have a completely normal pattern. These preliminary results seem to point out the fact that, at least in some patients with the Stein-Leventhal syndrome, there is an increased secretion of an androgenic steroid either from the adrenal or the ovary. Much more extensive steroid studies are now in process in this laboratory and will be reported later.

Summary. An evaluation has been made of 18 patients with polycystic ovaries and hyperthecosis diagnosed as such inside of 2 years in a general hospital.

Ten of the young women were below the mean age of 25 years. Only half of the patients were definitely overweight. Hirsutism, although difficult to evaluate, was present in all cases but certainly only of very minor degree in 3 of them. The most constant menstrual irregularities were oligohypomenorrhea and periods of amenorrhea dating back to the menarche in two-thirds of the patients. Two women presented with a history of menometrorrhagia. Twelve of the 13 married women had been sterile.

The ovaries were greatly enlarged in only 8 cases. In all the other patients, the ovarian size was around the upper limit of normal. The major histological findings were: thickened tunica albuginea, microcysts, hyperthecosis and stroma hyperplasia in some cases.

All patients, except one, responded to bilateral ovarian wedge resection with normal menstrual periods. Three pregnancies have occurred during the 27-months follow-up period. Absolutely no change in the hirsutism has been noted in any of the patients following operation.

The only hormonal finding that may be of some significance is a mean urinary 17-ketosteroid value 4.2 mg. higher than the mean for normal women.

Chromatographic separation of the urinary 17-ketosteroids was done in 8 patients. Three were found to have an increased excretion of androsterone + etiocholanolone, one an increased level of dehydroepiandrosterone and the 4 others had a completely normal pattern. It seems that, at least in some patients with polycystic ovaries and hyperthecosis, there may be an increased secretion of an androgenic steroid either from the adrenal cortex or the ovary.

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SUMMARIO IN INTERLINGUA

Le Syndrome de Ovarios Polycystic e Hyperthecosis Un Evalutation Clinic

Esseva evalutate le casos de 18 patientes con ovarios polycystic e hyperthecosis, diagnosticate intra 2 annos in un hospital general.

Dece del juvene feminas habeva minus que le etate medie de 25 annos. Solmente un medietate del patientes habeva definitemente peso excessive. Hirsutismo—que es difficile a evalutar—esseva presente in omne le casos, in 3 clarmente a grados solmente minissime. Le plus constante irregularitates menstrual esseva oligo-hypomenorrhea e periodos de amenorrhea depost le tempore del menarchia in duo tertios del patientes. Duo del feminas habeva un historia de meno-metrorrhagia. Dece-duo del 13 maritate feminas in le serie habeva essite sterile.

Le ovarios esseva grandemente allargate in solmente 8 del casos. In omne le alteres, le dimensiones ovarial esseva in le region del limite superior del norma. Le major constatationes histologic esseva spissification del tunica albuginee, microcystes, hyperthecosis, e hyperplasia stromal in certe casos.

Omne le patientes, con un exception, respondeva al bilateral resection cuneate del ovarios per normal periodos de menstruation. Durante le 27 menses del periodo de observationes de controlo posterior, 3 pregnantias ha occurrite. Absolutemente nulle alteration del hirsutismo esseva notate in ulle del patientes post le operation.

Le sol constatation hormonal que es possibilemente de signification es un valor medie de 17-cetosteroide in le urina excedente per 4,2 mg le valor medie in feminas normal.

Separation chromatographic del 17-cetosteroides in le urina esseva effectuate in 8 del patientes. Esseva trovate que 3 habeva un augmento del excretion de androsterona-etiocholanolona. In 1, le nivello de dishydroepiandrosterona esseva elevate. In le 4 alteres, le valores esseva completemente normal. Il pare que al minus certes del patientes con ovarios polycystic e hyperthecosis ha un augmento del secretion de un steroide androgenic, o ab le cortice adrenal o ab le ovario.

THE CEREBRAL PERIPHERAL CIRCULATORY ACTION OF NYLIDRIN HYDROCHLORIDE*

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Recently it has been reported that nylidrin is a useful agent for increasing the circulation to the peripheral muscular areas of the body (Hensel, Ruef and Golenhofen[2], Klasson[5], Pomeranze *et al.*[8], Riddel, Steel, McCoy[10], Stein[11]). There is considerable need for such an agent for the treatment of ischemic night pain and intermittent claudication. Most of the presently available drugs (tolazoline and nicotinic acid) have their effects primarily on the skin circulation. The purpose of the present report is to describe the circulatory effects of nylidrin hydrochloride in man and animals, and its use in the management of peripheral and cerebral arterial insufficiency.

Nylidrin is 1-(p-hydroxyphenyl)-2-(methyl-3-phenyl-propylamino) propanol hydrochloride and the formula is shown in Fig. 1.‡

Fig. 1.—Chemical formula of nylidrin hydrochloride.

Methods and Materials. Twenty-five patients with arteriosclerosis involving the lower extremities were studied. All patients were ambulatory and had intermittent claudication and other symptoms of ischemia of the limbs. In no case was gangrene present. The patients averaged 48 years of age with a range of 30 to 74. In addition, studies were carried out on 11 rabbits. Pulse rate was measured by auscultation and in a few cases by the Colson

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blood pressure apparatus. Cardiac output was measured using radioactive iodinated serum albumin with a scintillation counter over the heart, the recordings being made on a recording rate meter. Ballistocardiograms were made on a standardized Nickerson low frequency bed. Clearance of I_{131} from muscle was studied with a scintillation counter over the site of injection in calf muscle after 2 microcuries were injected deeply into the muscle (Rapaport *et al.*[9]). Calf flow was measured plethysmographically with the triple cuff technique (Hyman and Winsor[3]) and this was checked with a water plethysmograph of the Barcroft type[1]. Peripheral resistance of vertebral arteries and later employing a drop counter which measured blood flow into the internal carotid artery. Clearance of iodine from gray and white matter was studied also (Kety[4]). Measurements in man were made after an appropriate period of rest before the drug and again after the drug, a second reading being taken at the height of the maximum pulse rate which was recorded continuously with the cardiotachometer. The results were recorded in terms of the per cent of the control values. In all cases the parenteral studies were made before and after 5 mg. of nylidrin intramuscularly or intravenously. The results of the parenteral studies are shown in Table 1.

TABLE 1.—THE EFFECT OF NYLIDRIN EXPRESSED AS A PER CENT OF THE CONTROL VALUES

	No. Pts.	*Average**	*Range**
CARDIAC EFFECTS			
Pulse rate	10	122	105 to 158
Blood pressure (mm.Hg)	10		
Systolic		104	100 to 111
Diastolic		90	84 to 95
Cardiac output	8		
Minute volume		122	111 to 133
Stroke volume		108	101 to 115
Ballistocardiogram			
Height of IJ wave	5	134	118 to 175
PERIPHERAL VASCULAR EFFECTS			
Clearance of I_{131} from muscle, %/min.	5	160	130 to 210
Calf flow, ml./100 ml./min.	10	189	140 to 250
Peripheral resistance, calf, in units	10	50	28 to 68
Finger flow, c.mm./sec.	10	118	110 to 128
Toe flow, c.mm./sec.	10	108	102 to 114
RENAL PLASMA FLOW			
Flow, ml./min.	11	83	60 to 97

*All values as % of the controls

the calf was determined by measuring the blood pressure at the popliteal space by auscultation. The mean pressure was determined by adding the systolic pressure to two times the diastolic pressure and this value was divided by three. The peripheral resistance was determined by dividing the mean pressure by calf flow in ml. per 100 ml. of limb per minute. Finger and toe flows were measured plethysmographically employing digital occluding cuffs. In animals muscle flow was measured with a drop counter which measured the rate of inflow of blood into the femoral artery (Knapp, Hyman and Bercel[6], Lindgren[7]). The skin of the limb was dissected away so that only muscle flow was measured. Renal plasma flow was measured with para-amino hippuric acid using the constant infusion technique. Cerebral flow was measured in rabbits by first tying off the

In addition, 20 patients were given oral Nylidrin, 6 mg. three times daily, to determine side effects, if any. These dosages were employed because they are therapeutic and have been found to be well tolerated. Room temperature for all studies averaged 23° C. plus or minus 2°.

The intensity of the heart tones was studied using a Sanborn microphone with suitable amplification, the analysis being made on the Panoramic Subsound Analyzer.

Results. CARDIAC EFFECTS. The cardiac effects are shown in Table 1. The pulse rate increased in all cases and to a significant degree. The systolic blood pressure increased slightly and the diastolic pressure decreased. The cardiac output (minute volume) showed

a definite increase and the stroke volume increased slightly. The ballistocardiograms showed an increase in the amplitude of the I-J wave (Fig. 2). The intensity of heart sounds was studied in 5 patients after the parenteral injections of 5.0 mg. of the drug. is shown in Fig. 4. The increase was considerably greater than in control studies which were carried out before and after the injection of saline. Calf muscle flow was increased on the average. The maximum increase was to 2.5 times the control. An example is

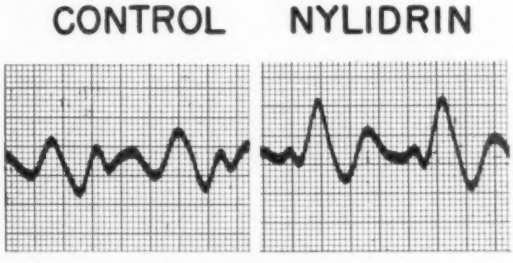

Fig. 2.—Ballistocardiograms before and 15 minutes after the intravenous injection of 5 mg. of nylidrin.

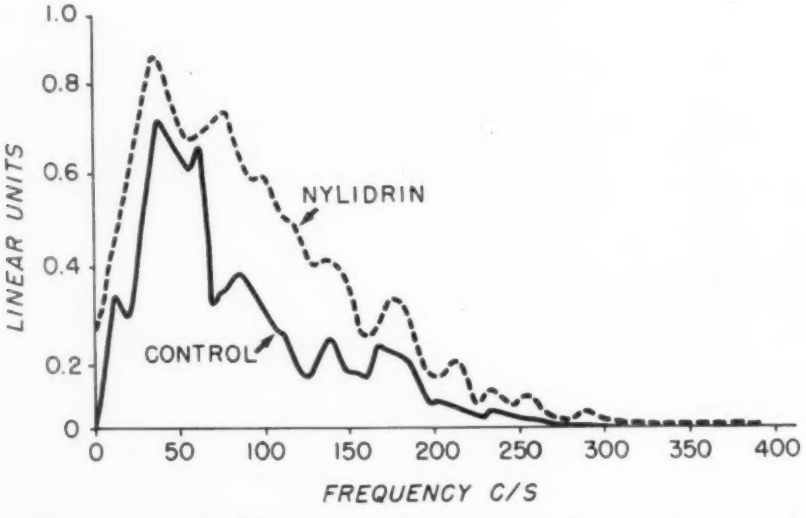

Fig. 3.—Frequency analysis of the heart sounds in a patient before and 15 minutes after the intravenous injection of 5 mg. of nylidrin.

In all cases the intensity increased in all frequency ranges, the maximum increase being from 75 to 125 cycles per second (Fig. 3).

PERIPHERAL VASCULAR EFFECTS. Clearance of I_{131} from muscle was definitely more rapid after nylidrin. An example shown in Fig. 5. The peripheral resistance showed a distinct drop as there was a slight drop in mean popliteal artery pressure and an increase in calf flow. Finger blood flow showed, on the average, a moderate increase. Toe flow increased to a slight extent.

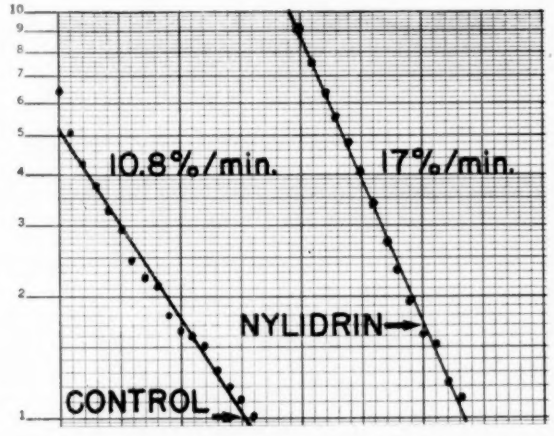

Fig. 4.—Clearance of I_{131} from calf muscle of a patient before and 20 minutes after 5 mg. of nylidrin intramuscularly.

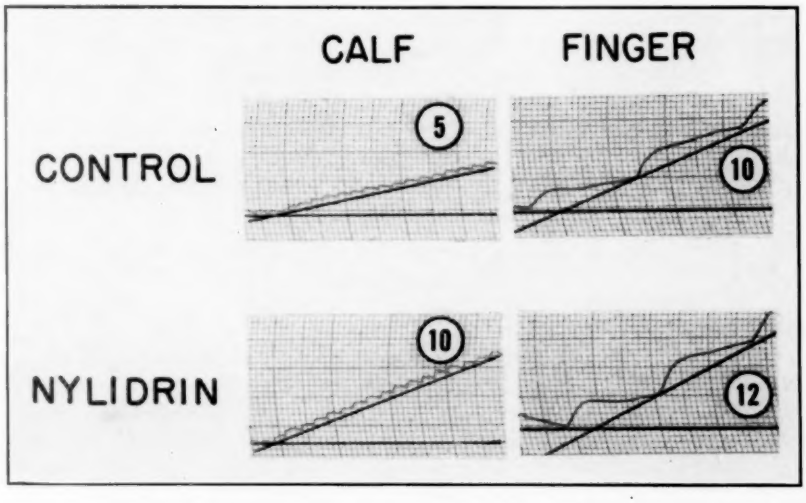

Fig. 5.—Calf flow and finger flow in a patient before and 20 minutes after the intramuscular injection of 5 mg. of nylidrin.

The blood flow in the calf muscle of the rabbit was studied in 12 animals (Table 2). All animals were anesthetized with urethane and all remained in good condition throughout the entire experiment. The nerve supply to the muscles was left intact. The leg was skinned and the foot was tied off. There was a definite increase in femoral artery flow. The percentage increase averaged 50.0. The mean arterial blood pressure fell by an average of 8.5%. There was a decrease in the peripheral resistance of 36.4%.

RENAL PLASMA FLOW. This was decreased slightly in all cases but was not great enough to be significant.

CEREBRAL CIRCULATION IN THE RABBIT.

This was studied in 10 rabbits. The intra-carotid infusion of one microgram per kilo body weight per minute of nylidrin produced an average increase in flow of 49% in the internal carotid artery. The value approximated the average increase in clearance rate arterial pressure averaging less than 5%, indicating a reduced cerebral vascular resistance.

Despite a tendency for both carotid flow and clearance rate to return towards the control state during prolonged infusion of the agent nylidrin

TABLE 2.—THE EFFECT OF NYLIDRIN ON THE CIRCULATION OF RABBIT MUSCLE. I = INITIAL VALUE AND A = AFTER NYLIDRIN

Dosage	*Femoral Art. Flow*$_I$ *(ml./min.)*	*Femoral Art. Flow*$_A$ *(ml./min.)*	*% Chg.*	*Mean Art. B.P.*$_I$ *mm.Hg*	*Mean Art. B.P.*$_A$ *mm.Hg*	*% Chg.*	*PVR*$_I$	*PVR*$_A$	*% Chg.*
5γ/k./min.	5.35	2.40	+76.0	76	73	— 3.5	142	77	—45.5
10γ/k./min.	4.05	5.85	+44.0	76	75	— 1.3	188	128	—31.9
10γ/k./min.	4.30	5.60	+30.0	71	70	— 1.4	165	125	—24.2
10γ/k./min.	3.00	4.15	+38.0	70	63	—10.0	234	152	—35.1
10γ/k./min.	3.25	4.05	+25.0	68	62	— 8.8	210	158	—24.8
10γ/k./min.	5.35	7.50	+40.0	80	66	—17.5	150	88	—41.4
10γ/k./min.	5.85	14.65	+150.0	95	80	—15.8	162	55	—66.1
10γ/k./min.	5.50	7.15	+30.0	80	80	0.0	146	112	—23.3
10γ/k./min.	7.50	13.35	+78.0	82	73	—11.0	109	55	—49.6
10γ/k./min.	9.75	12.0	+23.0	80	77	— 3.7	82	64	—22.0
5γ/k./min.	3.75	5.30	+41.5	78	70	—10.2	208	132	—36.6
5γ/k./min.	4.80	6.10	+27.0	74	60	—18.9	154	98	—36.4

B.P. = blood pressure
I = before injection
A = after injection
PVR = peripheral vascular resistance

TABLE 3.—THE EFFECT OF NYLIDRIN ON CEREBRAL CIRCULATION IN THE RABBIT

No. of Animals	*Inj. Site*	K_I	K_A	*% Chg.*	*M.A. B.P.*$_I$ *mm. Hg*	*M.A. B.P.*$_A$ *mm. Hg*	*% Chg.*	*Int. Carotid Flow*$_I$ *(ml./min.)*	*Int. Carotid Flow*$_A$ *(ml./min.)*	*% Chg.*
5	Int. cap.	0.0358	0.0556	+60.1	84.2	82.0	—3.0	1.66	2.30	+49.0
5	Caud. nuc.	0.1059	0.1539	+47.5						

M.A. = mean arterial
B.P. = blood pressure
K = clearance
I = before injection
A = after injection

of I_{131} obtained simultaneously from a representative area of gray matter (claudate nucleus), and was somewhat less than the increase of clearance rate from white matter (internal capsule) (Table 3). The increase in the two parameters in response to nylidrin was accompanied by a fall in mean arterial pressure averaging less than 5%, indicating a reduced cerebral vascular resistance.

Despite a tendency for both carotid flow and clearance rate to return towards the control state during prolonged infusion of the agent nylidrin functioned as an effective vasodilator of the cerebral blood vessels in the rabbit.

CLINICAL STUDIES. Twenty-five patients were studied for clinical effects. Five of these patients had lightheadedness or vertigo, mental confusion or diplopia and murmurs over the caro-

tid arteries or other evidence of cerebral vascular insufficiency and on placebos the symptoms were not improved: however when nylidrin was given some of the symptoms were partially alleviated. The intravenous and intramuscular injections were well tolerated. There was no thrombosis at the site of the injection nor was there evidence of venous irritation. The oral administration of the drug in the doses employed did not produce gastrointestinal symptoms. Palpitation was encountered occasionally. Postural hypotension was not seen in any case. Angina pectoris which existed previously in some of the patients was not aggravated. Ischemic night pain was improved in 4 of 6 patients with arteriosclerosis obliterans.

Discussion. Nylidrin in doses of 5 mg. intramuscularly or intravenously was well tolerated as was 6 mg. orally three times daily. Only occasionally did patients complain of palpitation with the oral administration and in no case did this appear detrimental to patients. The drug was of particular value clinically in relieving some of the symptoms of cerebral vascular insufficiency (vertigo, lightheadedness, mental confusion, diplopia) and studies on the rabbit brain showed that there was an increase in cerebral vascular flow and an increased clearance of radioactive I_{131} from both the white and gray matter of the brain. In addition, the agent proved of value in relieving night cramps when these were of ischemic origin. There was definite evidence of increased circulation through the muscle of the calf of man and rabbit; however clinically improvement from intermittent claudication was difficult to evaluate because the observations must of necessity be subjective. It is of interest that the skin vascular bed showed a slight increase in circulation in the region of the fingers and toes. Studies of renal circulation showed that the renal plasma flow dropped slightly as blood was diverted into the muscular areas of the extremities. Also, cardiac rate and minute volume and to a lesser extent the stroke volume increased, probably as a response to the drop in mean and diastolic pressure which serves as a regulating mechanism to maintain the circulation in as many vascular beds as possible. There is, however, evidence of local peripheral vascular dilatation in the region of calf muscle as shown by the decrease in peripheral resistance which occurs in this area. The increased cardiac output and the decreased peripheral resistance following nylidrin hydrochloride both favor increased circulation to the extremities.

It is of interest that none of these patients exhibited postural hypotension although theoretically this might occur. It would seem that this drug would have a definite field of usefulness in cerebral vascular insufficiency as suggested by the increased cerebral circulation in the rabbit and the decrease in dizziness and other signs of cerebral ischemia in man.

Summary. It has been shown in experimental animals and in man that nylidrin hydrochloride increases blood flow in the muscle of the calf and brain and to a minimal extent in the fingers and toes. Also there is an increase in cardiac output (minute volume and stroke volume). Nylidrin hydrochloride produced symptomatic clinical improvement when used in the management of cerebral vascular insufficiency and ischemic leg night pain.

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SUMMARIO IN INTERLINGUA

Le Effecto de Hydrochloruro de Nylidrina in le Circulation Cerebral e Peripheric

Esseva monstrate in animales experimental e in humanos que hydrochloruro de nylidrina augmenta le fluxo de sanguine in le musculo del sura e in le cerebro e a grados minimal in le digitos de pede e mano. Il etiam occurre un augmento del rendimento cardiac (*i.e.* del volumine per minuta e del volumine per pulso). Hydrochloruro de nylidrina produceva un melioration del symptomas clinic quando illo esseva usate in le tractamento de insufficientia cerebrovascular e de nocturne dolores ischemic in le gamba.

SUMMARIO IN INTERLINGUA

(See page 609 for original article)

Darenthina: Un Nove Droga Anti-Hypertensive Reporto Preliminari

1. Darenthina es un potente agente anti-hypertensive.

2. Su effectos anti-hypertensive es le plus marcate in position erecte; illos es minus impressionante in le positiones jacente e sedente.

3. Es recommendate que iste droga es addite al regime anti-hypertensive quando methodos a reduction de sal es inefficace o quando le effectos anti-hypertensive es desirate urgentemente.

AN EXPLORATION OF THE ANTIHYPERTENSIVE ACTION OF CHLOROTHIAZIDE

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AND

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Chlorothiazide† differs from nonbenzothiadiazine diuretics by virtue of its antihypertensive effect as well as its propensity to induce excessive urinary losses of potassium. Potassium depletion has been shown to lower blood pressure in normal (Freed and Friedman[8]) or hypertensive rats (Friedman, Rosenman and Freed[12]), and to lessen smooth muscle (Henrikson[16], Webster, Henrikson and Currie[31]) and peripheral vascular tone (Friedman, Freed and Rosenman[11]). Although chlorothiazide also lowers peripheral vascular reactivity (Beavers and Blackmore[3]) it does not reduce a normal blood pressure (Freis *et al.*[10]).

The mechanism by which chlorothiazide reduces elevated blood pressure has not been elicited despite intensive investigation. It seemed possible that the antihypertensive effect of chlorothiazide might be mediated through potassium depletion. To test this hypothesis, we administered the drug to a previously untreated hypertensive patient for 6 weeks of a controlled metabolic balance study. Potassium repletion during the last 2 weeks of the study did not cause any elevation of blood pressure reductions obtained with chlorothiazide.

Methods and Materials. A 51-year-old, 60 kg. white man, who had a sustained hypertension of 200/140 to 180/115 mm. Hg throughout a 3-month period of hospitalization, was the subject of this study. He had no history or evidence of congestive heart failure, a normal blood urea nitrogen and excretory urogram, negative urine cultures and urinary sediment, a urine specific gravity of at least 1.022, and had never been treated for his hypertension. After intensive investigation had revealed no other diagnosis than "essential hypertension," he was transferred to the metabolic balance ward.

A metabolic balance technique standard in this department was employed (Plough *et al.*[21]). The patient was first equilibrated for 4 days and then observed on a constant liquid diet containing 35 cal. per kg., 1.2 gm. of protein per kg., 120 mEq. of sodium (2 mEq. per kg.), and 60 mEq. of potassium (1 mEq. per kg.) each day, with added multivitamin supplements. Fluids were given *ad libitum*. Following equilibration and a 7-day control period, chlorothiazide therapy was begun in a dosage of 500 mg. twice daily and continued for 6 weeks. During the fifth week, potassium losses were repleted by adding 20 mEq. per day (given orally as potassium lactate) to the diet, and during the final week 4 mEq. per day of additional maintenance potassium were given. Potassium repletion dose was determined by averaging daily potassium loss in the treatment period. Urine was collected for daily analysis during the control, repletion, and maintenance periods, and in 4-day pools during the 28-day therapy period. Stools were collected in 7-day pools, apportioned with alternating car-

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†6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide. Trade name: Diuril.

mine and charcoal markers, throughout the entire study. Blood samples were secured twice weekly.

Urine was analyzed for sodium, potassium, carbon dioxide, chloride, creatinine, ammonia nitrogen, pH and titratable acidity. Feces were analyzed for sodium, potassium, and chloride. Blood was analyzed for sodium, potassium, carbon dioxide combining power, chloride, blood urea nitrogen, uric acid, and creatinine. All analyses were performed by standard techniques (Knowlton *et al.*[18]). The total body content of potassium was determined five times weekly in the whole body liquid scintillation counter (Anderson[2]).

ses were performed by current laboratory methods (Knowlton *et al.*[18]). Renal blood flow (RBF), and renal afferent and efferent arteriolar resistances were calculated using published formulae (Lamport[19]).

Results. The blood pressure declined rapidly in the first 7 days of chlorothiazide administration, and then became stable at levels of 140 to 145/100 to 105 mm. Hg. There was no increase in the blood pressure during the potassium repletion and maintenance periods; if anything, a still further slight decrease occurred (See Fig. 1).

There was an immediate increase in the urinary excretion of sodium, potassium, and chloride of approximately one week's duration after chlorothiazide (See Table 1). Thereafter, the excretion of these electrolytes remained close to control values. With potassium replacement and maintenance, a second rise in urinary potassium occurred along with slight increases in urinary sodium and chloride. Chlorothiazide

TABLE 1.

		Chlorothiazide Administration					
Substance	*Control Week*	*1st Week*	*2nd Week*	*3rd Week*	*4th Week*	*5th Week K 20 mEq./d Added*	*6th Week K 4 mEq./d Added*
Urinary K Aver. mEq./day	48	68	48	45	49	67	58
Urinary Na Aver. mEq./day°	113	137	84	114	119	120	118
Urinary Cl Aver. mEq./day°	95	159	80	100	107	110	102
Urinary pH	5.5	5.7	5.9	6.1	6.0	6.0	6.0
Blood Urea Nitrogen mg./100 ml.	13, 11	18	22	22	14	15	15
Serum Uric Acid mg./100 ml.	3.2	5.8	5.3	5.2	5.2	5.9	4.7

°Exclusive of days on which special renal function studies were done.

Blood pressures were secured by auscultation, always by the same physician or nurse, at 0700, 1200, and 1800 hours daily, in the prone, sitting, and standing positions. Electrocardiograms were secured every other week.

Special studies of renal tubular function and renal hemodynamics were done; once in the control period twice in the therapy period, and once in the potassium maintenance period. These included glomerular filtration rate (GFR), measured as inulin clearance, renal plasma flow (RPF), measured as para-aminohippurate (PAH) clearance, and tubular excretory mass (Tm), measured as Tm PAH. These were performed according to standard techniques (Smith[27]), and analy-

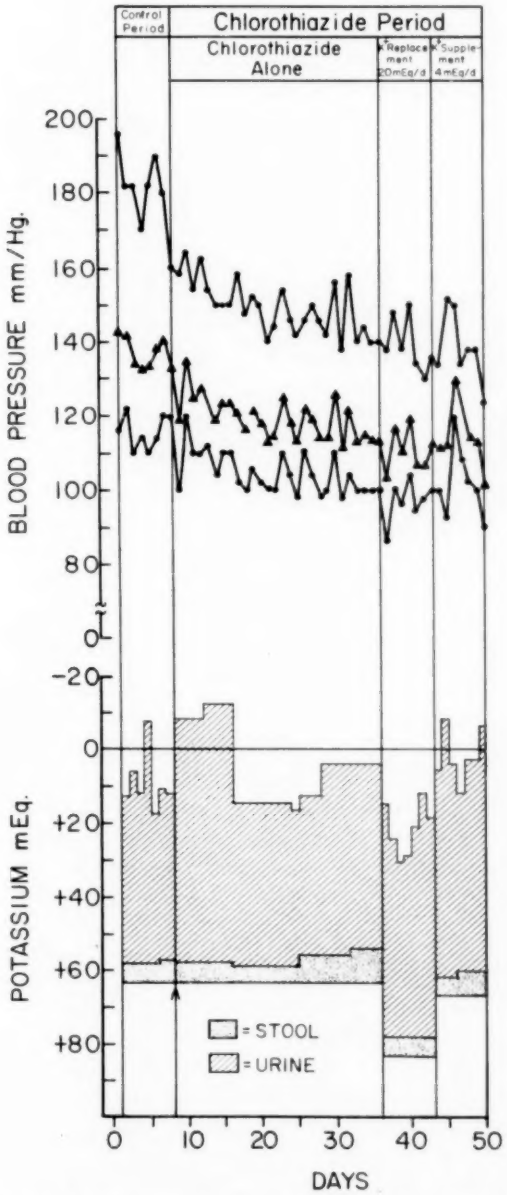

Fig. 1.—A comparison of the potasium balance and the blood pressure response. The balance is plotted with total intake of potassium extending downward from the zero line, and total excretion of stool and urine potassium plotted upward from the maximum intake. Shaded areas above the zero line represent a negative balance, while unshaded areas below the zero line represent a positive balance. The blood pressure is plotted (from top to bottom), as systolic, mean, and diastolic.

administration was also accompanied by a gradual rise in urinary pH and bicarbonate, but no essential changes were noted in urinary ammonia nitrogen, titratable acidity, or in the fecal excretion of electrolytes.

The measurements of potassium balance (Fig. 1) showed a total net loss (over control values) of potassium of only 110 mEq., almost all of which took place in the first week. Thereafter, a slowly increasing retention of potassium occurred until balance was restored during the repletion period. There was no change in the serum potassium during the entire study. The whole body liquid scintillation counter, useful for determining total body potassium content (Anderson[2]), showed no detectable change during the study. This was not unexpected, since the magnitude of change in this patient was within the counting error of the machine.

A loss of 158 mEq. of body sodium developed in the first 4 days of chlorothiazide therapy. Thereafter, a trend toward retention of body sodium occurred which decreased the cumulative loss to 100 mEq. after 4 weeks of continuous chlorothiazide. Potassium repletion and maintenance did not influence sodium excretion appreciably in the final 2 weeks.

There were no significant variations in the measurements of serum sodium, carbon dioxide combining power, hematocrit, total protein, chloride, or creatinine. The blood urea nitrogen and serum uric acid rose transiently during chlorothiazide therapy.

RENAL TUBULAR FUNCTION. In the control period, the patient had an essentially normal glomerular filtration rate, tubular excretory mass, renal plasma flow, and filtration fraction (See Fig. 2). The GFR decreased 48% by the fourth week of chlorothiazide therapy, while the tubular mass remained constant. Since renal plasma flow remained almost constant, a decrease in filtration fraction accompanied the fall in GFR (FF = GFR/RPF). All values returned to or towards normal during the potassium repletion and maintenance periods.

RENAL HEMODYNAMICS. There was an initial increase in renal blood and plasma flow, when chlorothiazide was initiated (See Fig. 2). Both values returned to control measurements during the therapy period, and remained constant during the potassium repletion-maintenance periods. Arteriolar resistance dropped, in both the afferent and efferent arterioles. However, these resistances did not return to normal during the potassium periods, remaining considerably below their control values (See Fig. 2).

Discussion. The mechanism of action of chlorothiazide in reducing elevated blood pressures does not appear to be related to a depletion of body potassium, at least over a 6-week period of observation. Our patient lost 110 mEq. of potassium, and had a concomitant fall in blood pressure from a mean pressure of 135 mm. Hg to a mean pressure of 115 mm. Hg, but his blood pressure did not rise when his potassium loss was repleted over a 7-day period, or when he was given maintenance potassium to equal his anticipated daily loss for another 7 days. Our observations on the electrolyte excretion pattern following chlorothiazide administration parallel the results of others (Ford, Moyer and Spurr[7], Magid and Forsham[20]).

Intensive investigation has not yet yielded the mechanism of action of chlorothiazide in reducing elevated blood pressures, although valuable negative information has been gained. It has been suggested that chlorothiazide acts by reducing the urinary excretion of ganglionic blocking agents (Haring-

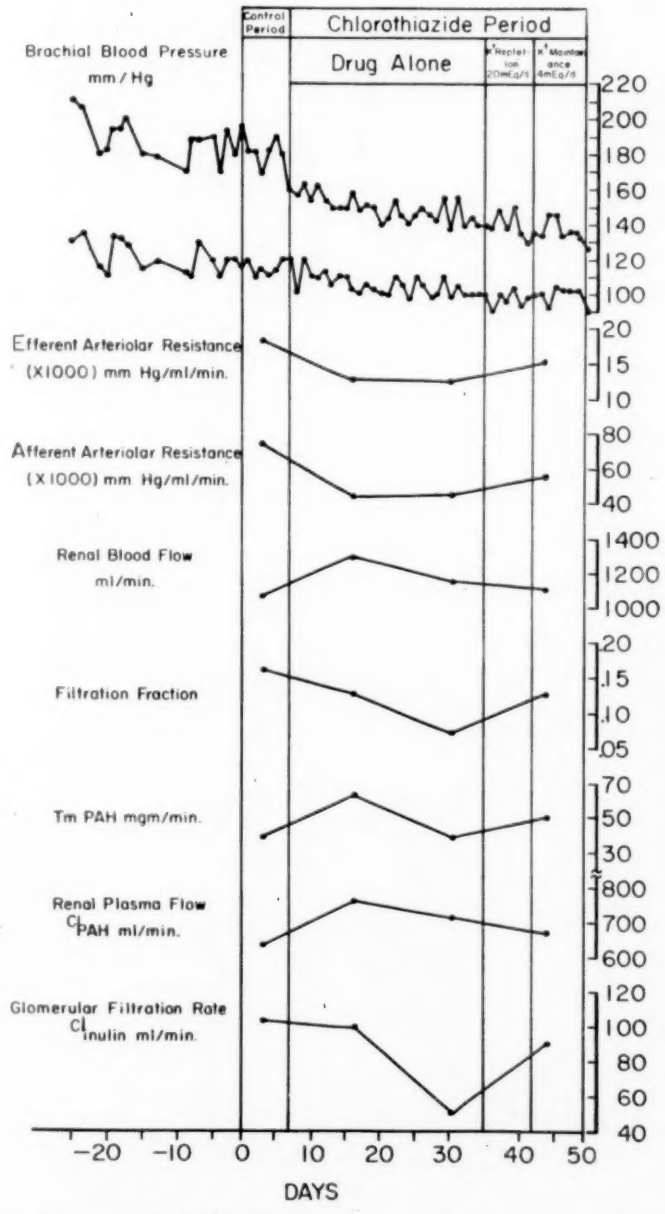

Fig. 2.—A comparison of the blood pressure response and the parameters of renal tubular function and renal hemodynamic function.

ton and Kincaid-Smith[15]), or by depleting the body of sodium (Tapia *et al.*[30]), and conversely, (Hollander and Chobanian[17], Wilkins[32]) has an action which cannot be explained by sodium depletion. Although it is a potentiator of ganglionic blocking agents, chlorothiazide is not thought to be a blocking agent itself (Freis *et al.*[9]). It has been found to reduce cardiac output (Crosley *et al.*[6]), and to decrease plasma and extracellular fluid volume (Wilson and Fries[34]). Reports of falls in glomerular filtration rate of up to 50% (Corcoran *et al.*[5], Crosley *et al.*[6], Magid and Forsham[20]) and elevations of BUN during chlorothiazide therapy were confirmed in this study. It has been stated that chlorothiazide does not depend upon intracellular electrolyte changes for its effectiveness, although it may be a renin depleter (Wilkins, Hollander and Chobanian[33]). Chlorothiazide appears to cause a decrease in peripheral vascular responsiveness to infused cathachol amines (Beavers and Blackmore[3]).

Previous studies have demonstrated that the renal hemodynamics of essential hypertension are characterized by an increased efferent arteriolar resistance (Goldring *et al.*[14]). This increase in resistance is reversible by various means, and accompanies a fall in blood pressure (Goldring and Chasis[13]). Our study has demonstrated such a fall in efferent arteriolar resistance, as well as in afferent arteriolar resistance. However, that this is the basis of the mechanism of action of chlorothiazide, cannot be deduced from these results. Previous postulation of the cause of the decreased arteriolar resistance has suggested that a "humoral pressor agent" has been blocked (Smith *et al.*[28]); such a thesis remains unproven. The hypothesis that essential hypertension is a manifestation of relative renal ischemia (Goldring and Chasis[13]) is not supported by our study, since the renal blood flow returned to control values, without any change in blood pressure.

Potassium has been implicated previously in hypertension (Rahman *et al.*[22]), renal disease (Schwartz[26], Spargo[29]), myocardial fibrosis (Schrader, Prickett and Salmon[25], Robinson *et al.*[23]), and myocardial insufficiency (Aikawa and Fitz[1], Clarke and Mosher[4]). Experimental potassium depletion by dietary restriction will lower the blood pressure of normal (Freed and Friedman[8]) and hypertensive (Friedman, Rosenman and Freed[12]) rats. There is also a decreased peripheral vascular response to pressor amines in the potassium depleted rat (Rosenman, Freed and Friedman[24]), which will return to normal upon potassium repletion (Friedman, Freed and Rosenman[11]). Despite the results of our short term study, it may be that the long term effect of chlorothiazide is to decrease body potassium, lower peripheral resistance, and thus cause a drop in systemic blood pressure.

In our patient, during chlorothiazide administration, afferent and efferent renal arteriolar resistance decreased, with secondary increases in the renal blood flow, functioning tubular mass, and a secondary decrease in the glomerular filtration rate. During the potassium repletion period the renal blood flow, tubular mass, and GFR returned to or towards normal, but the arteriolar resistance remained significantly lowered. Potassium depletion in man will cause a fall in the GFR (Schwartz[26]), but usually only when the depletion is greater than occurred in our patient. Also, the decreased GFR of potassium depletion is accompanied by a decreased tubular mass, which we did not find. It does not seem likely that these changes in renal function are due to potassium

depletion alone, even though this is suggested by their return toward control levels during potassium repletion. If potassium depletion were the sole cause, then arteriolar resistance should also have returned to normal; such was not the case. The observed responses during chlorothiazide therapy are consistent with renal hemodynamic adjustments to a decreased arteriolar resistance. The return toward normal of all parameters of renal function studied, except arteriolar resistance, may have been a function of renal compensatory adjustments to the decreased arteriolar resistance. We are left then with the finding that the renal arteriolar resistance is lowered by chlorothiazide therapy, for reasons not known to us.

This study has shown that chlorothiazide reduces renal arteriolar resistance. The relation of this finding to the basic mechanism of action of chlorothiazide in reducing an elevated blood pressure has not been demonstrated. Over a 6-week period of time, a reduction of total body potassium (to the degree achieved in this study) appears unrelated to the ability of chlorothiazide to reduce an elevated blood pressure.

Summary. Chlorothiazide is a unique diuretic in that it causes a marked loss of body potassium and reduces an elevated blood pressure. It was postulated that the ability of the drug to lower blood pressure might be related to its kaliuretic effect.

A previously untreated 51-year-old patient with uncomplicated "essential hypertension" was studied by means of the metabolic balance technique, and treated with chlorothiazide. His blood pressure was reduced by the drug and he had a concomitant loss of 110 mEq. of body potassium. Repletion of potassium losses did not affect the reduced blood pressure.

Measurements of renal function and renal hemodynamics revealed a fall of the glomerular filtration rate while the drug was being administered. This returned toward its control value when the patient was repleted with potassium. Renal plasma flow and tubular excretory mass remained normal throughout. The renal afferent and efferent arteriolar resistances decreased while chlorothiazide was being administered, but did not increase again when potassium was repleted. The relationship of the decreased renal arteriolar resistance to the primary mechanism of action of chlorothiazide cannot be proven, but is not a function of a decrease in body potassium.

ACKNOWLEDGMENTS: We would like to express our gratitude to Lt. Col. E. G. Herndon, Jr., MC, for suggestions during the early part of this study; to Captain Barbara Baggs, ANC, for nursing assistance; to Captain Bernard Balikov, MSC, and Mr. Gerald McCormick, for supervising laboratory procedures; to Captain Mildred Duomi, AMSC, for supervising diet preparation, and to Mrs. Doris Blackmon for secretarial assistance.

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(Interlingua on page 577)

DARENTHIN: A NEW ANTI-HYPERTENSIVE DRUG PRELIMINARY REPORT

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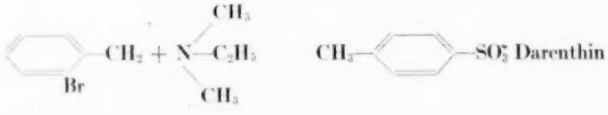
A low salt low saturated fatty acid diet with or without sedation is the present-day preferred treatment of persons with high blood pressure (Palmer[3]). Unfortunately, many of the severer grades of high blood pressure do not respond to this regimen and there are malignant forms that require rapid control to avoid disastrous complications or death. It is for these reasons that search continues for drugs which will more effectively reduce high blood pressure as well as for the fundamental mechanisms which produce these states.

Boura, Green, McCoubrey, Lawrence, Moulton and Rosenheim[2] have introduced a new type of hypotensive agent, Bretylium tosylate or N-O-bromobenzyl-N-ethyl: N : N-demethyl-ammonium p-toluensulphonate.



It is one of a series described by Boura, Copp and Green[1] which block selectively the peripheral sympathetic (adrenergic) nervous system without antagonizing the effects of released or injected adrenalin or norepinephrine. No depression of the parasympathetic or central nervous system is said to occur. The drug accumulates selectively in the adrenergic neurons. It is this selective action which suggests that it may be more effective in reducing blood pressure and also that it may produce less side effects than the ganglion-blocking drugs.

In order to determine the anti-hypertensive effects of this drug* as rapidly as possible, persons with high blood pressure were chosen who had been under treatment for at least 2 years. They had not responded to the basic anti-hypertensive regimen with the addition of ganglion-blocking drugs or had failed to continue on such regimens because of untoward side effects.

Material and Methods. There were 14 persons, 10 males and 4 females, 37 to 71 years of age. All had grade 2 or 3 retinopathy of the Keith-Wagener classification. All had electrocardiographic abnormalities consistent with left ventricular hypertrophy. None had elevated blood ureas or gross urinary abnormalities. All knew that they had high blood pressure and were familiar with the anti-hypertensive regimens previously used. Four accepted the new medication reluctantly. Eight were pleased with the prospects of a new effective drug. A double blind procedure was regarded as unnecessary because the effects of the drug were related presumably to body position. No dietary restrictions were

*Kindly supplied by Burroughs Wellcome and Company.

used except for the absence of table salt which had become customary for these persons.

The initial dose was 100 mg. given every 8 hours as recommended by Boura *et al.*[2]. At the end of one week, if a satisfactory orthostatic effect was not produced, each dose was raised by 100 mg. and after 2 more days by 50 mg. until symptoms or orthostatic hypotension appeared. The smallest amount effectively producing orthostatic hypotension was maintained for the remainder of the experimental period that lasted 2 to 4 weeks.

At the end of the experimental period 2 patients were placed upon a 400 mg. sodium diet and 500 mg. chlorothiazide. The potentiating effect of this regimen on the orthostatic hypotensive dose of Darenthin was determined.

TABLE 1.—DATA ON BLOOD PRESSURE BEFORE AND 2 TO 4 WEEKS AFTER THE BEGINNING OF AN EFFECTIVE ORTHOSTATIC HYPOTENSIVE DOSE OF DARENTHIN

				Initial Blood Pressure mm. Hg			*Final Blood Pressure mm. Hg*		
Name	*Sex*	*Age Years*	*Final Dose mg./day*	*supine*	*sitting*	*standing*	*supine*	*sitting*	*standing*
J.F.	M	50	600	190/126	186/122	194/120	170/110	160/106	120/80
J.W.	M	42	1200	160/114	164/118	170/122	160/100	162/104	140/92
F.W.	M	54	1500	220/140	210/136	216/140	220/140	194/120	150/96
S.S.	M	69	1800	210/128	206/122	212/118	190/110	176/110	160/100
M.S.	M	62	750	184/118	196/122	200/128	170/116	150/102	136/84
M.R.	F	36	900	220/140	220/140	210/136	180/110	170/100	100/60
C.L.	F	46	900	190/122	182/118	192/118	170/112	166/110	130/92
M.J.	M	49	750	140/122	142/118	138/124	136/112	132/104	132/88
A.H.	F	37	600	180/122	182/118	190/124	174/112	166/108	140/92
H.G.	M	45	300	220/140	210/136	224/140			
K.C.	F	68	600	200/120	200/118	206/114	190/114	174/108	148/86
B.B.	M	56	1200	180/110	184/112	192/120	172/108	158/106	140/94
M.C.	M	53	900	180/120	200/140	180/120	160/110	156/104	150/90
F.S.	M	71	900	240/126	232/124	240/130	180/110	160/100	120/70

Results. The results are summarized in Table 1.

After being on 100 mg. Darenthin 3 times a day for 3 days, one patient (H.G.) complained of itching eyelids that were red. He refused to continue taking the drug because he believed he was allergic to it. The other 13 completed the trial.

One (F.W.), a physician, developed stuffiness in his nose immediately after lying down at bedtime. This symptom was abolished by taking the last dose 3 hours before bedtime. Four developed easier bowel movements. They were delighted with this reaction in contrast to the uncomfortable constipation produced by ganglion-blocking drugs. The only other symptoms were those associated with orthostatic hypotension.

Weakness and lightheadedness were frequent with marked orthostatic hypotension. One complained of an indescribable odd sensation in the occipital region. Another had a sensation apparently akin to giddiness. Strangely, weakness in some was particularly pronounced when first arising in the morning. In others, weakness was more marked late in the afternoon. All symptoms could be abolished quickly by diminishing the dose and yet maintaining significant orthostatic hypotension.

There were no significant changes in the clinical status of the heart, electrocardiogram, eye grounds, urine or in the blood urea.

The effective orthostatic hypotensive dose varied from 600 to 1800 mg. Most responded to 800 to 900 mg. daily in three divided doses. The effective dose bore no relation to the height of the untreated blood pressure or any other finding. The impression was created that the more high-strung person required a larger dose.

Orthostatic hypotension was achieved in each person. Occasional escapes to

low hypertensive levels were present. The orthostatic hypotensive effect was not related to the changes in blood pressure obtained in the supine or sitting position. As a rule, pressures in these positions remain in the hypertensive levels although frequently the pressures tended to be 10 to 20 mm. lower (both systolic and diastolic) than the pretreatment level. However, marked orthostatic hypotensive levels were seen without any significant change in the sitting and supine position. Furthermore, the hypertensive state can appear the instant the supine position is assumed. Thus one (F.W.) had a pretreatment blood pressure of 220/140 which, during treatment, fell to 150/96 while standing and instantly returned to 220/140 when recumbency was assumed.

Two were subsequently placed upon 500 mg. chlorothiazide daily and a 400 mg. sodium diet. The dose of Darenthin needed to produce orthostatic hypotension could be reduced from 900 mg. to 300 mg. in one and from 1500 mg. to 600 mg. in the other. With this regimen supine blood pressures were lower than with the previous regimen but commonly still in the low hypertensive level and rarely within normal limits.

Discussion. This preliminary study confirms Boura's report that Darenthin is a potent anti-hypertensive drug which produces few side effects other than those due to the lowered blood pressure. Its effect can be potentiated by saluretic agents. It is superior therefore to the ganglion-blocking drugs. Like the latter, however, it is not an ideal anti-hypertensive agent because the supine and sitting blood pressures may be affected but slightly. The occasionally wide and almost instantaneous swings in pressure with change in position may possibly be dangerous to the vascular system.

For these reasons, it is suggested that Darenthin should be used as an adjunct in the therapy of the hypertensive state. It should be used when the basic low salt, low saturated fatty acid diet with saluretic agents and with or without sedation is ineffective and when the clinical status requires immediate or rapid relief. These combinations are more effective and may diminish the wide swings in blood pressure with change in body position which may occur when Darenthin is used alone.

One patient apparently developed an allergic reaction to the drug. The possibility of drug toxicity and tachyphylaxis will have to await more prolonged studies on a large number of patients.

Conclusions. 1) Darenthin is a potent anti-hypertensive agent.

2) Its anti-hypertensive effects are most marked in the upright position and less impressive in the supine and sitting positions.

3) It is suggested that this drug be added to the anti-hypertensive regimen when salt depleting methods are ineffective or when anti-hypertensive effects are urgently needed.

ADDENDUM: Since completing this paper, 3 additional patients fulfilling the above criteria have similarly responded to Darenthin.

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(Interlingua on page 600)

STUDIES ON THE ROLE OF THE RETICULOENDOTHELIAL SYSTEM IN HURLER'S DISEASE*†

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Hurler's disease has been recognized as a clinical entity since 1917. The first two patients were described by Hunter[11] in 1917, and the next report by Hurler[12] appeared in 1919. Commonly used synonyms for this disorder are gargoylism and lipochondrodystrophy.

The symptoms and physical findings in a typical case are characteristic and are summarized in Table 1. The most striking of these are physical and mental retardation, enlargement of the skull, corneal opacities, thickness of the tongue, short stubby fingers, hepatosplenomegaly, and umbilical hernia. These are shown in Figs. 1 and 2. Roentgen-ray findings, when present, are definitive and are summarized in Table 2. Representative examples are shown in Fig. 3.

Life expectancy for patients with Hurler's syndrome is diminished with few surviving beyond their middle teens. Death is usually attributed to either upper respiratory tract infections or cardiac failure.

TABLE 1.—CHARACTERISTIC SIGNS AND SYMPTOMS OF HURLER'S DISEASE

Signs:	• Enlargement of the Skull
	• Corneal Opacities
	• Thick Lips and Tongue
	• Flaring of the Lower Rib Cage
	• Cardiomegaly With or Without Auscultatory Findings
	• Prominence of the Abdomen
	• Hepato-Splenomegaly
	• Umbilical and Inguinal Herniation
	• Kyphosis with Gibbus of Dorsal-Lumbar Spine
	• Short Stubby Fingers
	• Limitation of Extensibility of Joints
Symptoms:	• Mouth Breathing
	• Recurrent Upper Respiratory Infections
	• Visual and Auditory Defects
	• Mental Retardation with Behavior Problems—Delayed Sitting, Walking and Talking and Poor Bladder and Bowel Control

The possible hereditary aspects of this disorder have been postulated by Nja[22], Jervis[13], Halperin and Curtis[8], Beebe and Formel[1], Cunningham[3] and

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McKusick[17]. Their studies suggest that this disorder has both an autosomal and sex-linked recessive mode of genetic transmission.

Jervis[13] reported several cases and reviewed the literature of Hurler's syndrome in which he felt cases with incomplete and less striking clinical manifestations often escape recognition. He felt that these "formes frustes" are perhaps more numerous than the "typical forms" of the disease.

TABLE 2.—ROENTGEN-RAY FINDINGS

Large Scaphocephalic Skull
Prominence of Frontal Bones
Heavy Supraorbital Ridges
Bossing of Temporal Bones
Increased Length and Shallowness of Sella Turcica
Kyphosis of Dorsal-Lumbar Spine ("Beaking")
Wedge-Shaped Deformities of Lumbar Vertebrae
Osseous Growth Disturbances Most Prominent in Upper Extremities

Though there has been intensive investigation of various aspects of this disorder, the hematological features have received little attention. It is the purpose of this report, therefore, to record the blood and bone-marrow observations made in patients with Hurler's syndrome and to draw attention to an apparently unique inclusion present in certain bone-marrow cells of these subjects.

Material and Methods of Study. A. PATIENTS. This study consists of 14 patients with Hurler's disease diagnosed on the basis of clinical and roentgenographic findings and included 8 males and 6 females whose ages ranged from 4 months to 16 years.

Eleven of the 14 patients were studied at the James Whitcomb Riley Children's Hospital, and their physical and roentgenographic findings conformed with those described by others (See Table 1). Detailed clinical records were not available for those of the patients who were institutionalized at another State Institution.

B. HEMATOLOGICAL OBSERVATIONS. Of the 14 patients in this study 11 had single or multiple peripheral blood examinations. Five of this group had recorded platelet values. Though Reilly[23] had reported finding leukopenia in a majority of their patients, we have no recorded instance of significant leukopenia. We noted moderate to marked anemia in 3 patients. In no instance did we observe thrombocytopenia. On differential examination of the peripheral blood, 2 patients demonstrated a very mild lymphocytosis with 2700 and 4500 mature lymphocytes per c.mm., respectively. We were unable to demonstrate in peripheral circulating leukocytes the lilac-staining bodies described by Reilly[23] though, as will be described later, these were occasionally seen in bone-marrow preparations.

Single or multiple bone-marrow specimens were obtained from 12 of the patients in this group. All marrows were studied with supravital stain in a manner described by Sabin[24]. Pull slip preparations were obtained, and from these, permanent Wright's stained specimens were prepared. Additional marrow pull slip preparations were subjected to various differential histochemical stains, as described below.

The striking abnormality that we observed in these marrow preparations related to the fixed tissue histiocytes hereafter designated as phagocytic clasmatocytes. Within the cytoplasm of these cells were noted characteristic inclusion bodies which in our experience, have not been demonstrated in any other condition. In both supravital and Wright's stained preparations, these had a comparable appearance. The inclusion consisted of a stained central body with a surrounding clear zone. The stained body varied from coccoid to rod-shaped, measured 0.2 to 4 micra in the long axis and stained varying shades of red from violaceous to orange red in color. Each cell contained from 20 to 50 of these inclusion bodies. Occasionally, in the bone marrow these inclusions were also observed in lymphocytes, plasma cells and reticulum cells. The morphological characteristics of these inclusions are illustrated in Figs. 4 and 5, and we have arbitrarily designated these inclusion-bearing clasmatocytes as "Hurler's cells."

C. HISTOCHEMICAL STUDIES. In an effort to identify the chemical nature of the abnormal inclusion material several histochemical stains were employed. Pull slip preparations of bone marrow previously air dried and fixed in methyl alcohol for 3 to 5 minutes were used from the 12 patients with Hurler's disease. Control pull slip preparations of bone marrow from normal individuals were stained histo-

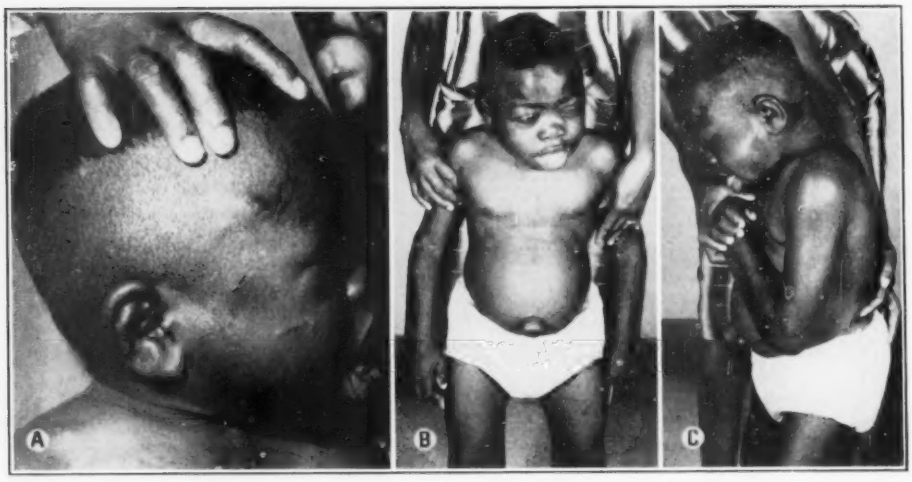

Fig. 1*a*, *b* and *c*.—W.B., age 9 years. The enlarged head, protruding large tongue, depressed nasal bridge, short neck, protruberant abdomen and umbilical hernia are typical stigmata of Hurler's disease.

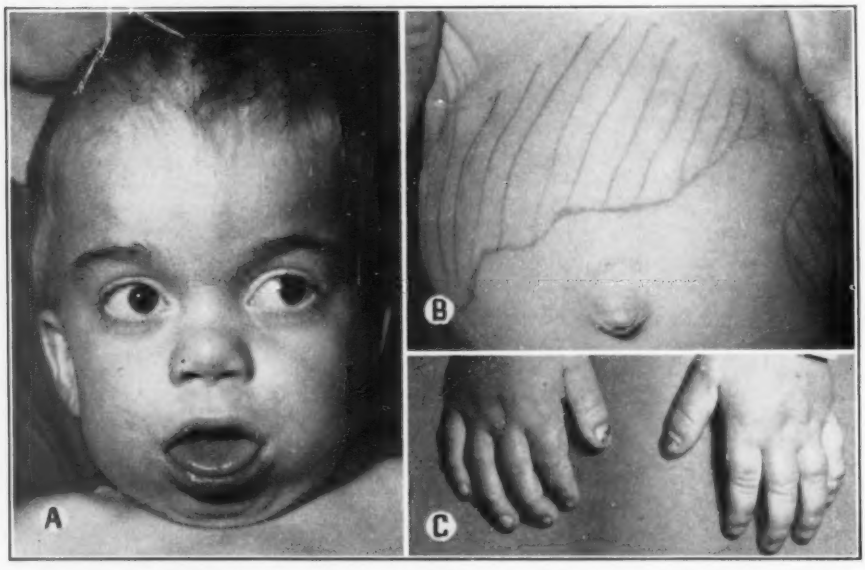

Fig. 2*a*, *b* and *c*.—M.H., age 3 years. In addition to the characteristic facies, this patient demonstrates the hepatosplenomegaly and short, stubby fingers commonly seen in Hurler's disease.

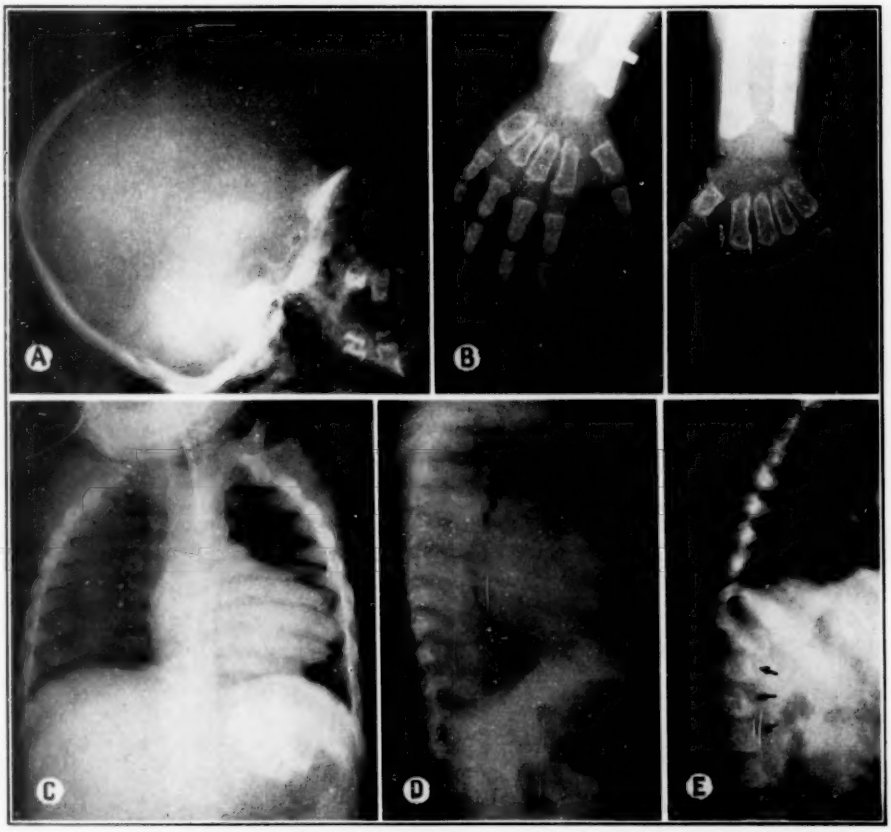

Fig. 3.—Characteristic Roentgen-ray findings of Hurler's disease in patient M.H. *a*) Enlarged skull and J-shaped sella turcica, *b*) Shortened radius and ulna, poorly developed carpal ossification and broad stubby metacarpels and phalanges, *c*) Cardiomegaly and widening and thickening of ribs, *d* and *e*) Beaking of lumbar vertebrae with kyphosis of dorsolumbar spine.

TABLE 3.—DIFFERENTIAL HISTOCHEMICAL STAINS EMPLOYED IN HURLER'S DISEASE

Stain	*Staining Affinity*	*Results in Hurler's Disease*
Periodic Acid Schiff Technique	Polysaccharide	Stained Inclusions
Buffered Thionin	Mucin	Stained Inclusions
Weigert's Iron Hematoxylin	?	Stained Inclusions
Oil Red O Sudan Black	Lipid	Did Not Stain Inclusions
Best's Carmine	Glycogen	Did Not Stain Inclusions

chemically at the same time with those preparations from patients with Hurler's disease. All preparations were subjected to the following histochemical staining techniques: periodic acid Schiff technique (Wislocki, Rheingold and Dempsey[27]), Weigert's iron hematoxylin (Lillie[14]), buffered thionin (Highman[10]), oil red O (Lillie and Burtner[15]), Sudan black (Lillie and Burtner[15]), and Best's carmine (Lillie[14]). Results are summarized in Table 3.

The observed inclusions in the Hurler's cells were stained by periodic acid Schiff, buffered thionin and Weigert's iron hematoxylin and neither the clear zone nor central body of the inclusions stained with oil red O, Sudan black or Best's carmine.

Characteristically, Weigert's iron hematoxy-

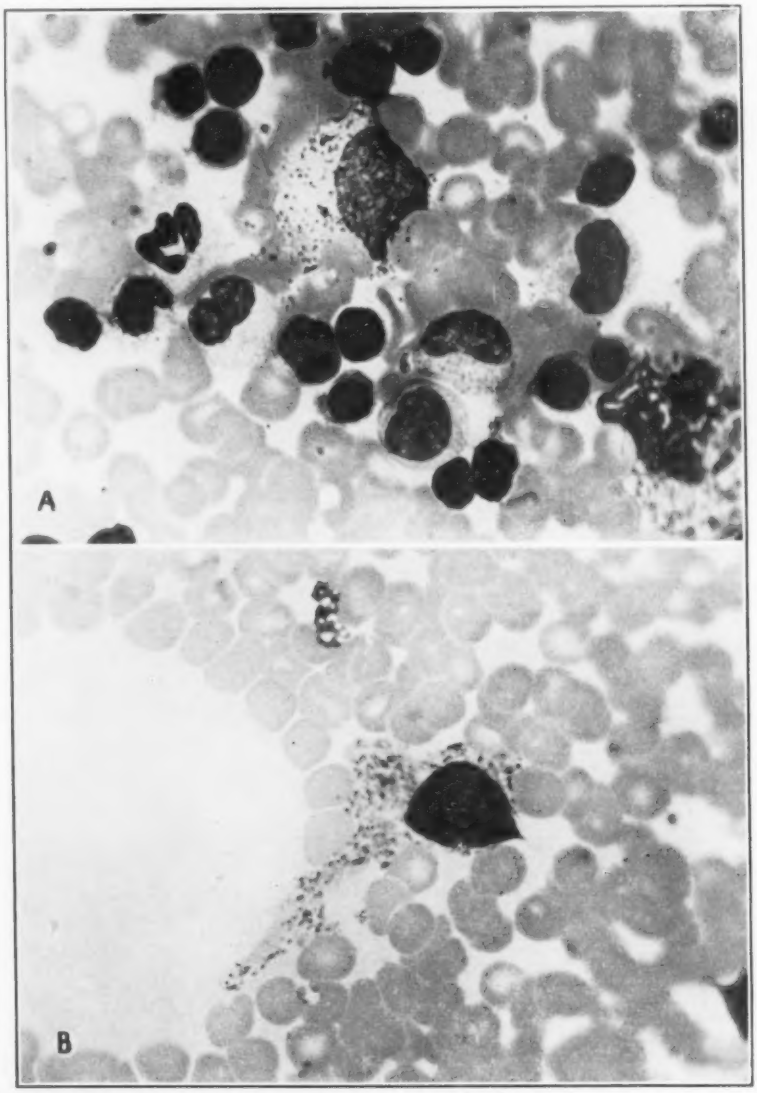

Fig. 4*a* and *b*.—Two typical "Hurler's cells" in bone marrow showing the characteristic inclusion bodies within the cytoplasm of the phagocytic clasmatocytes. Wright's stain × 900.

lin imparts a reddish purple coloration to mucopolysaccharide, and this color reaction was confirmed by staining the known mucopolysaccharide-containing granules of the mast cell at the same time marrow preparations from patients with known Hurler's disease were stained. Instead of this reddish purple coloration, the Hurler's cell inclusions stained an intense bluish-green. We are at a loss to explain this bluish-green staining reaction since the periodic acid Schiff and the buffered thionin stains had given a positive staining reaction for mucopolysaccharide. It is possible that the Weigert's iron hematoxylin might have been fixed by material in the surrounding clear zone of the inclusion body masking the mucopolysaccharide staining central body.

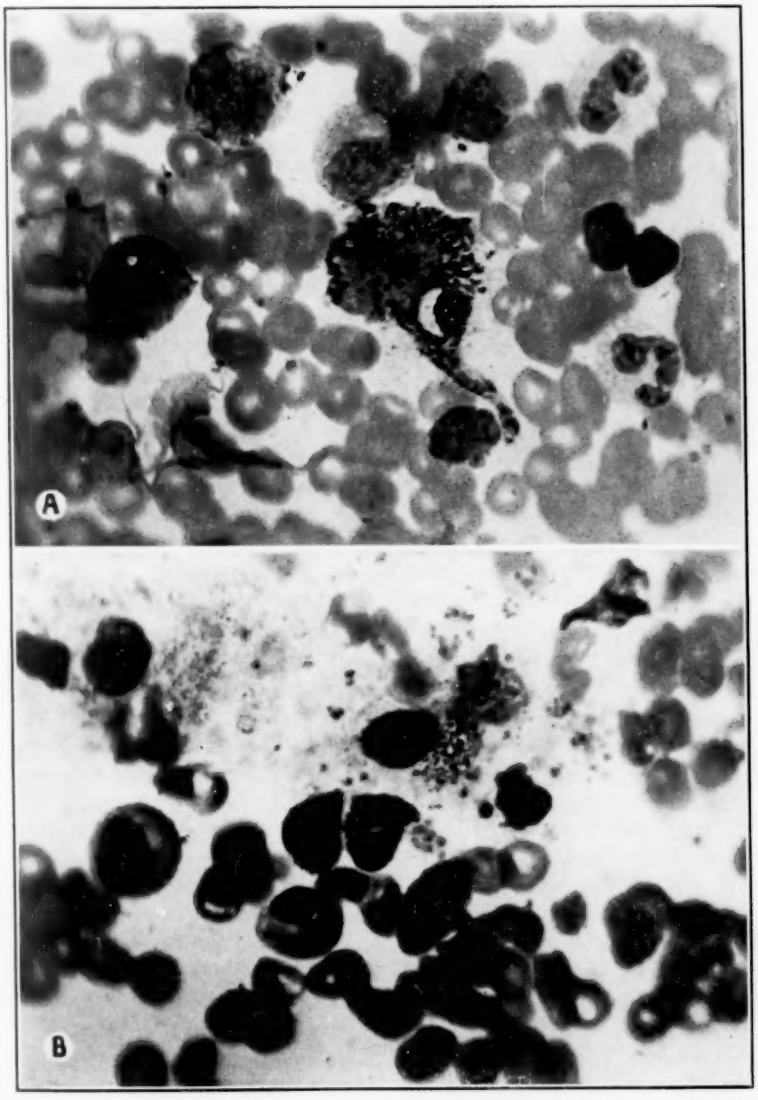

Fig. 5*a* and *b*.—Two "Hurler's cells" from bone marrow of different patients. The clear zones surrounding the stained central bodies are clearly shown. Note the large clear zone in Fig. 4*a* surrounding a large central body resulting from a condensation of several smaller inclusions. Wright's stain × 900.

Discussion. Little attention had been given to the hematological aspects of gargoylism until 1941 when Reilly[23] described a dark lilac granulation in the cytoplasm of the neutrophilic granulocytes when stained with Giemsa-Wright's technique. He observed these inclusions both in the peripheral blood and in the bone marrow of 4 patients with Hurler's disease. These lilac granules were also occasionally seen in lymphocytes and monocytes. Reilly described only the morphological and cytological appearance of these granules and felt that they were produced by the cell and did not represent phagocytized material.

These observations on the lilac granulations were confirmed by Lindsay *et al.*[16], who observed such inclusions in the mature leukocytes of the peripheral blood of patients with Hurler's disease. It was his observation that such granulations were found infrequently in the bone marrow.

Gasser[6], however, in 1950, mentioned such inclusion granules in bone marrow histiocytes; Zellweger, Giaccai and Firzli[28], subsequently, in 1952, reported 3 patients with Hurler's disease demonstrating lilac granulations in the leukocytes of the peripheral blood and in the reticulum cells, the osteoblasts and the histiocytes of the bone marrow.

Most recently, Griffiths and Findlay[7] reported their hematological observations in 2 brothers suffering from Hurler's disease. They were unable to detect abnormal lilac colored granular inclusions in the circulating leukocytes, but they did report abnormal inclusions in histiocytes and what they believed to be plasma cells. The inclusions in the histiocytes were granular masses varying in size from 1 to 2 micra in diameter, distending the cytoplasm of the cells, and, in some areas, lying free. The inclusions found in the possible plasma cells were described as ring-shaped with a clear center, lying in a vacuole in the cytoplasm. Attempts to stain these 2 granule types with Nile blue sulphate and periodic acid-Schiff methods on formol-fixed preparations were unsuccessful.

It would seem that persons suffering from Hurler's disease may then demonstrate abnormal inclusion bodies in their circulating leukocytes and in certain of the marrow cell elements. These inclusions in the circulating leukocytes have been reported as being identical with those seen in Alder's hereditary anomaly of leukocytes (Mauri and Soldati[19]); though, all patients with Alder's anomaly do not have Hurler's disease. Conversely, it is evident that many, if not most patients with Hurler's disease fail to demonstrate the Alder anomaly (Griffiths and Findlay[7]).

Detailed studies of patients with Hurler's disease have demonstrated inclusions within Kupfer's cells of the liver (Henderson *et al.*[9]), phagocytic splenic cells (Lindsay *et al.*[16]), cells of the central nervous system (Magee[18], Millman and Whittick[21], Nja[22]), lining cells of the coronary and other arteries (Emanuel[5], Lindsay *et al.*[16], Strauss[25]) and mesodermal connective tissue (Lindsay *et al.*[16]). Definitive histochemical studies (Brante[2], Dawson[4], Meyer *et al.*[20], Uzman[26]) have suggested that this inclusion material is mucopolysaccharide in nature.

In 1955, when we first had opportunity to examine the bone marrow of a patient with Hurler's disease, we noted bizarre inclusions within the phagocytic clasmatocytes similar to those later illustrated so beautifully by Griffiths and Findlay[7]. When we were subsequently able to suggest a later confirmed diagnosis of Hurler's disease to our pediatric associates on the basis of our finding such inclusion-bearing cells, we became quite interested in the possible constancy of these cellular

findings, their diagnostic validity, and, ultimately, in the histochemical nature of such inclusions.

To this end we solicited the cooperation of the staff of the James Whitcomb Riley Hospital and the authorities of the Muscatatuck State School. A diagnosis of Hurler's disease was made in 14 patients seen at the Indiana University Medical Center and Muscatatuck State School. Eleven of these patients had peripheral blood examinations at the Indiana University Medical Center. In 12 of these patients, we personally obtained and examined their bone marrows.

It is of interest that the Alder anomaly was not observed in the peripheral leukocytes of any of these patients although several showed this phenomenon in the mature leukocytes, lymphocytes, monocytes and neutrophilic granulocytes of the marrow. In all 12 of the patients whose bone marrow we had opportunity to study, these inclusion-bearing phagocytes were encountered. In the supravital technique, which we employ (Sabin[24]), a marrow fragment is maintained intact under the cover slip. Aggregates of phagocytic clasmatocytes tend to cluster in intact marrow fragments; hence, such inclusion-bearing phagocytic cells were much more readily demonstrated by supravital stain technique than by the more widely used Wright's stain method. In no instance, however, were we unable to find typical "Hurler's cells" on examination of the Wright's-stained marrow preparations of any of these 12 patients with Hurler's disease.

It was evident on study using supravital staining technique that these inclusions were contained almost entirely within the cytoplasm of the phagocytic clasmatocytes. Occasional examples of plasma cells containing these inclusions were observed and, in 2 patients, these inclusions were observed in motile leukocytes, lymphocytes, monocytes, and neutrophilic granulocytes, and myelocytes.

In all instances the stained inclusions contained within the cytoplasm of phagocytic clasmatocytes and plasma cells were surrounded by a surrounding, haloed clear zone (Figs. 4 and 5). This was most readily observed in the supravitally stained preparations. It was further evident that the larger the inclusion the more evident was the peripheral halo.

It is our opinion, based on our observations, that, though the inclusions varied in size and shape, all were composed in the same manner of the same material, with the larger granules perhaps representing a coalescence of the smaller granules.

The central staining portion of these inclusions on differential histochemical staining took a positive stain with Schiff's periodic acid and buffered thionin techniques, but failed to take a positive stain with Sudan black and oil red O. From these observations it would seem probable that these granules are composed of mucopolysaccharides (Table 3).

Our preparations stained with Weigert's iron hematoxylin according to the technique described by Lillie[14], yielded unexpected results. With this preparation, the granules stained a striking blue-green coloration. Though, ordinarily, mucopolysaccharides demonstrate a bluish-red coloration on staining with Weigert's iron hematoxylin, it has been noted (Lillie[14]) that under certain alterations in technique mucopolysaccharides will stain a green color. To check our staining technique, we simultaneously stained marrow preparations from a patient with Hurler's disease with those from a patient whose bone marrow contained many mast cells. To our consternation, we found the mast cell granules dem-

onstrating a typical bluish-red coloration whereas the "Hurler's cells" demonstrated the same unexpected bluish-green coloration. Though we are unable to explain this phenomenon, it could be suggested that possibly the stain is fixed by some substance within the haloed, peripheral, clear zone which modifies the staining reaction in this fashion.

The staining reactions demonstrated by these granules are quite comparable to those observed on histochemical and chemical analysis of other histiocytic cells of the reticuloendothelial system of other organs of the body in Hurler's disease (Henderson *et al.*[9], Lindsay *et al.*[16]). Similar material has been found in leptomeninges (Magee[18]) of the central nervous system and increased amounts of mucopolysaccharide have been found in the urine (Meyer *et al.*[20]) of patients with Hurler's disease.

These findings would suggest that one of the abnormalities in this disorder may be the elaboration of excessive mucopolysaccharides.

One might speculate that this metabolic dysfunction might have a rather wide range of manifestation with the possibility that some members of a family in which there is one suffering from Hurler's disease might demonstrate mucopolysaccharide inclusions in their bone marrow without other stigmata of the disease. We were unable to find either Alder's anomaly or marrow "Hurler's cells" in 3 clinically normal relatives of one of our patients. This does not exclude the possibility that such findings might yet be made and would seem to be an area for further study of this phenomenon.

It is of interest that we were able to demonstrate these "Hurler cells' in a patient too young to manifest diagnostic radiological abnormalities.

Summary and Conclusions. The study of the bone marrow of 12 patients with Hurler's disease reveals the invariable presence of phagocytic clasmatocytes containing inclusions. These inclusions seem to be unique to this disorder. The inclusions varied widely in size and shape, but consisted of a central-staining body and a peripheral, unstained clear zone.

These inclusions were occasionally encountered in plasma cells and, in only one of the patients, in the lymphocytes, monocytes and neutrophilic granulocytes. This was the only patient in this series demonstrating the Alder body phenomenon.

The central staining body proved, by differential histochemical staining, to be a mucopolysaccharide, but our studies failed to define the constituents of the peripheral clear zone. An attempt was made to demonstrate such "Hurler's cells" in the bone marrow of the clinically unaffected mother, father, or sibling of one of these patients with Hurler's disease, but such could not be found. The appearance of these cells in the bone marrow would seem to antedate the appearance of other manifestations of this disorder.

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SUMMARIO IN INTERLINGUA

Studios in Re le Rolo del Systema Reticuloendothelial in Morbo de Hurler

Le studio del medulla ossee de 12 patientes con morbo de Hurler revelava le presentia invariabile de phagocytic clasmatocytos continente inclusiones. Il pare que iste inclusiones es unic in morbo de Hurler. Illos variava grandemente in lor dimensiones e in lor conformation sed consisteva de un corpore a tincturation central con un zona non-tincturate clar al peripheria.

Le inclusiones occurreva sporadicamente in plasmatocytos, in un del patientes etiam in le lymphocytos, monocytos, e granulcytos neutrophilic. Iste ultime patiente esseva le sol in le presente series qui exhibiva le phenomeno del corpore de Alder.

Le tincturate corpore central esseva identificate per tincturation histochimic differential como un mucopolysaccharido, sed nostre studios non succedeva a definir le constituentes del zona clar al peripheria. Esseva essayate demonstrar tal "cellulas de Hurler" in le medulla ossee del clinicamente non afficite matre, patre, e fraterno de un del patientes con morbo de Hurler, sed nulles esseva trovate. Il pare que le apparition de iste cellulas in le medulla ossee precede le declaration de altere manifestationes de iste disordine.

PROGRESS
OF
MEDICAL SCIENCE

RADIOLOGY

UNDER THE CHARGE OF

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ROENTGENOGRAPHIC MANIFESTATIONS OF DIABETES MELLITUS

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SINCE the introduction of insulin, the clinical management of diabetes mellitus has improved so greatly that patients with the disease are surviving for increasingly longer periods. As a result of this prolonged survival, a wide variety of organic changes and complications may eventually develop. Many of these pathological lesions produce roentgenological changes.

A perusal of the literature discloses many case reports and studies of certain individual entities. This paper reviews the more pertinent observations which have been described and points out some of the less well known Roentgen-ray features. The discussion is organized according to organ systems.

Bone and Joint Abnormalities. RETARDATION IN GROWTH. Diabetes, when it occurs in childhood, may produce retardation of skeletal growth. This is particularly so when the disease is uncontrolled or difficult to control. Radiologically, much retardation manifests itself by delay in the appearance of ossification centers* or in the fusion of these centers with their associated

*For assessment of epiphyseal growth, the schematic diagrams of Stuart[168] are most helpful for the first year of life; between 1 and 6½ years, Vogt and Vickers charts[177] may be used; thereafter, the data of Greulish and Pyle[62] and Todd and Flory[23] are useful.

diaphyseal shafts[72,178]. The extent of the delay is influenced markedly by the severity of the disease and may amount to several years[18]. With proper treatment, however, most diabetic children exhibit little or no disturbance in skeletal development.

Diabetes occasionally is associated in infancy and adolescence with dwarfism and hepatomegaly. This syndrome, first described in detail by Mauriac[105,106], presents the radiological manifestations of retardation of skeletal development, osteoporosis, and hepatomegaly, as well as the clinical findings of diabetes, short stature, delayed sexual development, abnormal fat deposition, moon-faced appearance, and vascular disturbances[65,66,85,100,132,139,178,186]. Hypopituitarism is difficult to differentiate from this syndrome and indeed may be related to it. Figure 1 (*A*, *B*, and *C*) illustrates a case of diabetic dwarfism in a 33-year-old man. Observe the generalized osteoporosis, the ununited ossification center of the iliac crest, the stunted metacarpals and phalanges of the hands, and the conspicuous transverse "growth arrest" lines of the femur. Note also the partially calcified femoral artery.

GENERALIZED OSTEOPOROSIS. The pathogenesis of osteoporosis associated with diabetes still remains unexplained. The pituitary gland and adrenal cortex, of prime importance in carbohydrate metabolism, are also involved in bone metabolism. Excessive conversion of protein into glucose, thought to be present in diabetes[1,17,71], and resultant negative nitrogen balance may deplete the protein matrix of bone[160]. Increased osteoclastic activity can occur with acidosis[11,112], but this change has not been directly proven for diabetes. A few instances of osteoporosis or osteofibrosis of hyperparathyroidism may be secondary to renal complications.

The radiological appearance of the osteoporosis is nonspecific and follows the pattern seen in other types of bone atrophy[152]. It has been observed in as many as 50% of diabetic adults and in 25% of diabetic children[73]. Its coexistence with arteriosclerotic calcification at an early age should suggest the diagnosis. There has been no correlation between the duration of the diabetes and the extent of the generalized bone porosis[73].

The porosis is usually first recognized in the thoracic and lumbar spine[136,148]. The vertebral end plates appear as thin white lines and the spongiosa is abnormally radiolucent with conspicuous vertical trabeculae. Later, the expanding intervertebral discs deform the vertebrae to produce flattening, wedging, and so-called "fish vertebrae." The end plates may undergo concave indentation, or the nucleus pulposus may prolapse into the vertebral bodies (Schmorl's nodes). Pathological fractures may occur, particularly in the lower dorsal and upper lumbar regions. The pelvis is often involved, and the skull less frequently.

In the long bones, the cortex undergoes thinning but remains well defined, in contrast to the rather wide, fuzzy, and ill-defined cortex of malacic bone disease[59]. In advanced cases, transverse lines of increased density are frequently observed. Although these lines may be seen in healthy children they become more prominent in radiolucent porotic bones with growth retardation. The lines usually are symmetrically located near the ends of the shafts, parallel to the epiphyseal plates. They often vary in length and width.

LOCALIZED BONE AND JOINT CHANGES. (a) *Changes due to infection.* In diabetics, acute and chronic infections of the soft tissues are well known complications which frequently involve the adjacent bones with chronic osteomyelitis. The feet are particularly prone

Fig. 1.—Bone and joint abnormalities in diabetes.

(*A*), (*B*) and (*C*), Diabetic dwarfism in 33-year-old man with hepatomegaly. Note the generalized osteoporosis; the ununited iliac crest epiphyses in *A*, the stunted metacarpals and phalanges and incompletely fused epiphyses of the hands in *B*, the conspicuous transverse lines and trabeculae of the femur, with partially calcified femoral artery in *C*.

(*D*) Diabetic neurotrophic joint, atrophic type. Completely disorganized metatarsophalangeal joints. Progressive bone destruction and deformity.

(*E*) Diabetic gangrene with subcutaneous gas-formation. Early osteomyelitis of first interphalangeal joint.

to be affected. The alleviation of such infection is often more difficult than in non-diabetics. Arterial insufficiency of the lower limbs seems to be a common predisposing factor[15].

Radiologically, soft tissue swelling is usually the only manifestation seen in the early stages of this complication. Large areas of ulceration, however, may cause other soft tissue defects. The presence of abnormal radiolucent gas shadows subcutaneously indicates the presence of gas-forming organisms (Fig. 1*E*). The earliest signs of bony involvement of the phalanges or metatarsals include 1) loss of normally distinct cortical margins and 2) localized and often patchy demineralization of the involved bone. Widespread osteoporosis throughout the bones of the feet, periosteal reaction, and sequestration occur relatively late in the infection. In the healing phase, excessive sclerosis often develops.

Insulin and antibiotic therapy have greatly reduced the incidence of advanced infections. In many instances, the radiological signs of infection occur in combination with the osseous changes of peripheral vascular disease and neurotrophic lesions, and are sometimes difficult to distinguish. Arteriography has been used with increasing frequency to evaluate the presence, location and extent of the circulatory disturbances underlying the localized osseous changes[95].

(b) *Neuropathic joint disease.* Peripheral diabetic neuropathy may produce the so-called "pseudo-tabetic joints"[28,83,146,150,151,185]. Their mechanism of production is similar to those seen in neurosyphilis, Raynaud's phenomenon, syringomyelia, poliomyelitis, and in injuries and tumors of the spinal cord[7,15,20,29,31,75,83,133]. The common features of these conditions is a loss of pain sensation. This results in undue repeated trauma which damages first the articular cartilage, and, eventually, the underlying bone. Marked soft tissue swelling of the joints is usually observed without the signs of acute inflammation[156].

Radiologically, two types of neuropathic joint have been described: a common hypertrophic or sclerotic type, and a less common atrophic type. In the early stages of the former, soft tissue swelling due to the vascular connective tissue pannus is all that is seen. Later, as the articular cartilage becomes destroyed, the joint spaces become narrowed and irregular. The denuded underlying subchondral bony structures become flattened and show dense subchondral sclerosis. The picture may resemble simple osteoarthritic degeneration. Subchondral cyst formation, however, does not occur in neuropathic joints[44]. Extreme degrees of spur formation and overgrowth may occur at the joint margins and loose joint bodies are common. The frequent presence of subluxation, due to relaxation of the ligaments, is rather characteristic of neurotrophic joints. Spontaneous fractures and extensive fragmentations are not uncommon. The process is usually progressive, but occasionally remains stationary for many years.

The atrophic type of neuropathic joint is characterized radiologically by marked osseous destruction and fragmentation without visible new bone or osteophyte formation (Fig. 1*D*). The distal ends of the phalanges and metatarsal bones are tapered and the heads and shafts may appear separated. This process of absorption may continue until the entire bone becomes invisible. Subluxations are common, and in the later stages, the joints may become completely disrupted.

The joint changes may be unilateral or bilateral[90]. The most frequent sites of involvement are the tarsal and

ankle joints. The knees are less often affected[32,46,158,163]. Only one instance of extensive involvement of the lumbar spine has been reported[187]; in this case, extensive destruction of several vertebrae with considerable bone production was observed at necropsy. The distribution of the joint involvement contrasts with that of neurosyphilis and syringomyelia, in which involvement of the spine, hip and knee joints is common and changes in the ankle and tarsal joints less frequent.

Other types of joint disease may accompany the diabetic process. In one series of 500 patients with gouty arthritis, 3.9% had associated diabetes mellitus, an incidence twice that of the expected rate[12]. Asymptomatic hyperglycemia associated with gout is even more frequent[180]. A family history of diabetes in patients with gout is common, and in one series the incidence was as high as 42%[80]. There is, however, no known relationship between rheumatoid arthritis and diabetes, although this subject has been extensively studied by Jaervinen of Finland[82].

Vascular Disease in Diabetes. The increased incidence and early onset of arteriosclerosis in diabetes[37,85,141] are well known. However, their explanation is still far from complete. The lesions of both atherosclerosis and Moenckeberg's medial sclerosis are encountered, and do not differ essentially from those seen in nondiabetics later in life as part of the aging process. Atheromatosis is encountered in the elastic structures of the aorta and in such small arteries as the coronary and cerebral vessels, whereas medial sclerosis is the predominant lesion of the muscular arteries including the femoral and popliteal[179]. The most advanced lesions are seen in diabetes of early onset, and where poor control of the disease has persisted over a prolonged period.

The cardiac and renal complications secondary to arteriosclerosis are now the chief cause of death of diabetic patients. In the pre-insulin era, about 64% of deaths were from diabetic coma, and coronary artery disease was responsible for only 15% of deaths. At the present time, however, 56% of diabetic fatalities are due to coronary artery disease[85]. The incidence of coronary thrombosis at necropsy is as high as 64%[85] even when death occurs in the 20- to 30-year age group[27,94]. When advanced arteriosclerosis or arterial occlusion is present in the lower extremities, one can usually infer the presence of widespread vascular disease which includes the coronary arteries.

Roentgenograms are helpful in detecting the presence and extent of the lesions of both atherosclerosis and medial sclerosis[129]. In 200 patients studied 20 years after the onset of diabetes in childhood, White[182] found evidence of vascular disease in 92%; visible arterial calcifications were demonstrated on Roentgen examination in 75%. The youngest patient in this series was 11 years old[86]. Arterial calcifications have not been detected prior to the fifth year of diabetes.

The intimal calcifications of atherosclerosis appear radiologically as multiple, irregular, well-defined plaques, often confined to one section of the vascular wall[95]. The most severe changes are apt to be seen in the descending thoracic and abdominal portions of the aorta. Slightly overpenetrated chest films usually are able to record the calcified atheromatous plaques within the intima of the arch and descending aorta. Elongation, tortuosity and dilatation of the aorta are also often seen in these cases[58]. The abdominal aorta, when examined on lateral views of the lumbar spine is often calcified (Fig. 2*B*). In one

study[2] this structure was calcified in 66% and the pelvic vessels in 73% of the cases; calcification of peripheral arteries was also observed in 76% of the patients studied.

In the extremities, intimal calcifications are most commonly seen in Roentgen-ray films of the thigh. They are frequently limited to the junction of the femoral and popliteal arteries in the adductor canal, or, when the lesions are more diffuse, they are more prominent in this location. Compared with the frequent involvement of the arteries of the lower extremity, arterial lesions of the upper extremities are rare. In 469 patients with diabetic gangrene[22], arterial occlusion of the fingers was observed in only 3. In typical diabetic gangrene of the feet, the indolent process is usually caused by partial or complete obstruction of the

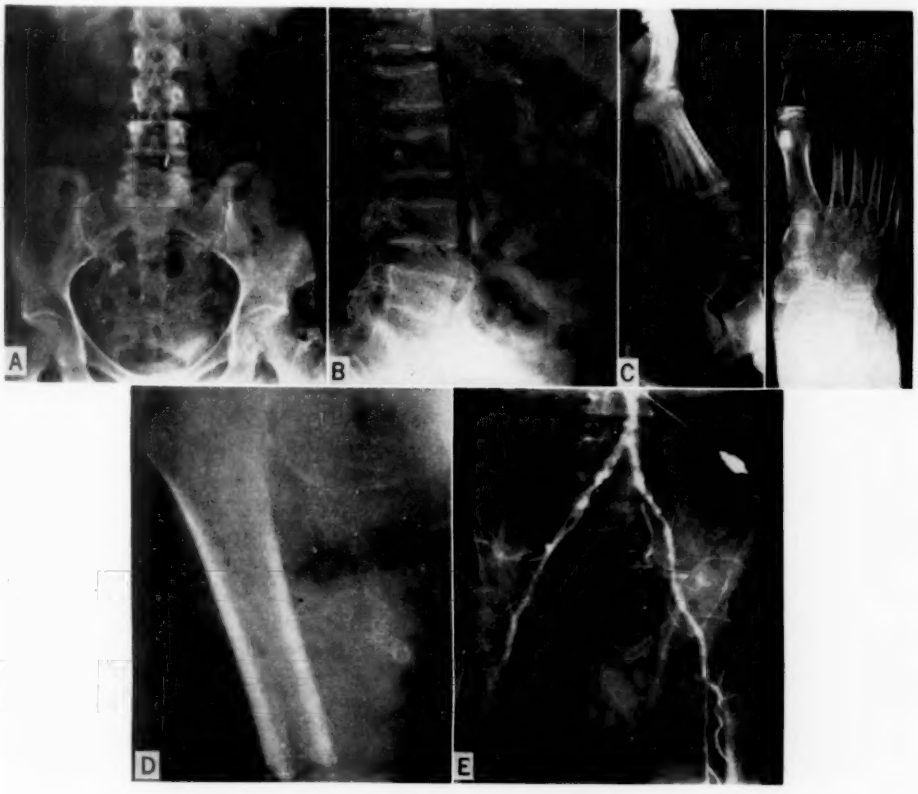

Fig. 2.—Vascular disease in diabetes.

(*A*) Advanced generalized arteriosclerosis with calcification of abdominal and pelvic arteries.
(*B*) Complete calcification of abdominal aorta in 33-year-old diabetic dwarf (See Fig. 1 A-C). Also pronounced osteoporosis of lumbar vertebrae.
(*C*) Calcified pedal arteries in 25-year-old diabetic. Osteoporosis of tarsals and phalanges.
(*D*) Continuous regular calcification in Moenckeberg's sclerosis with patent lumen. Amputation of mid-thigh.
(*E*) Lumbar aortogram. Advanced atherosclerosis of abdominal aorta, iliac arteries and obstruction of both superficial femoral arteries in 53-year-old diabetic patient.

digital arteries, and these usually show calcification.

Translumbar aortography or femoral arteriography are invaluable and relatively safe procedures for outlining the exact site and extent of atheromatous plaque formation, the presence of vascular obstruction and the degree of collateral circulation (Fig. 2*E*). Arteriography has been used in the selection of patients for arterial grafting by the Joslin Clinic since 1952[85]. Unfortunately, however, only a minority of arterial lesions in diabetics have been found suitable for grafting[31,91]. Postoperative arteriography has been used for re-evaluation, to determine the patency of the graft and to detect further progression of the disease. When plain films are compared with the arteriograms, it has been found that calcifications are present only where intimal thickening is greatest and encroachment upon the lumen most marked.

In medial sclerosis, calcium is deposited only in the musculature of the media. This change is a sequel to degeneration, swelling and fragmentation of the muscle fibers. The radiological appearance is accordingly quite different from that of atherosclerosis. The calcification is regular, diffuse and fine grained. In cross section, it appears as a smooth, well defined ring (Fig. 2*D*). Widespread distribution throughout the abdominal, pelvic and femoral arteries is common (Figs. 2*A* and *D*); the popliteal artery is somewhat less commonly affected. The association of medial sclerosis and atheromatosis is more common in diabetics than in nondiabetics. However, the two lesions are rarely encountered in the same arterial segment[31]. This is also true in experimentally produced arteriosclerosis[69].

In skull roentgenograms, the finding of premature calcification of the cavernous portion of the internal carotid artery, projecting over the sella (Figs. 5*B* and *C*), should suggest the diagnosis of diabetes in addition to such states as tertiary lues or metastatic calcification of hypercalcemia[107]. The calcification may be present in one or both internal carotid arteries and be patchy or striated in appearance.

In recent years, increasing attention has been paid to the lesions of the arterioles, capillaries and venules (diabetic microangiopathy) as the precursor of most forms of vascular disease[33, 56,111,165]. Unfortunately, at the present time, detection of these microscopic lesions by radiological means is not possible.

Disorders of the Digestive System. GASTROINTESTINAL ABNORMALITIES. Gastrointestinal disturbances are prominent features of many diabetic patients[125]. They occur mainly in two conditions: in diabetic coma or in the period preceding it, and in diabetic neuropathy involving the autonomic nervous system.

The onset of diabetic acidosis is often accompanied by the gastrointestinal symptoms of anorexia, nausea, vomiting and abdominal distress. The pain may be so severe that abdominal Roentgen-ray films are obtained, to rule out such "surgical" lesions of the abdomen as acute intestinal obstruction, perforated viscus, renal or biliary colic[125]. The distended stomach, with an air-fluid level, can usually be seen in the erect plain film of the abdomen. When barium is administered, the dilated stomach appears ptotic and usually extends below the level of the iliac crest when the patient stands in the upright position. The mucosal pattern is usually not visible, and decreased gastric motility is striking. Gastric retention of the barium may be prolonged for 24

hours or more. This gastric atony is thought to be the result of a central nervous system disturbance caused by the acetonemia. After recovery from the acidosis, the symptoms and radiological findings promptly subside.

Gastric retention is also encountered in a substantial group of diabetics who are not in acidosis, but who are difficult to control and have high insulin requirements[9,85,97,103,104,125,150,151,157]. These patients may complain of intractable diarrhea with nocturnal exacerbations or constipation sometimes alternating with diarrhea. Other symptoms suggestive of autonomic involvement may be present, including orthostatic hypotension, neurogenic bladder, impotence and defective sweating. An instance of gastric atony associated with visceral neuropathy and severe diabetes is shown in Figs. 3*A*, *B*, and *C*. Asymptomatic gastric retention is frequently seen[87] in young diabetics, on long-acting insulin, when the disease has been present for 3 or more years.

In the differential diagnosis of diabetes with gastric retention (gastroparesis diabeticorum), obstructing lesions of the antrum, pylorus and duodenal bulb must be ruled out. When the patient is examined in the prone, supine and oblique positions, the barium, in the diabetic, usually enters the duodenum passively and demonstrates a patulous pyloric canal. The gastric atony seen in diabetes is identical with that existing in other functional disturbances of the autonomic nervous system, including shock after severe injury or abdominal surgery, and following vagotomy[4,126,135].

Radiological abnormalities of the small bowel pattern in diabetes are not specific and the changes are quite variable in their degree of severity. The mucosal folds may become abnormally coarse and wide, usually first in the jejunum and later in other areas. There is frequently an abnormal variation in the caliber of the duodenum and other small intestinal loops. Segmentation of the barium is an almost constant finding, attributable both to the irregular expulsion of barium by the stomach and to the impaired peristaltic activity of the small bowel[169]. Delayed transit time[114] is observed in the majority of patients with either chronic diarrhea or severe constipation[74]. However, accelerated barium transit has also been observed occasionally[97]. The symptomatic relief from gastrointestinal symptoms, obtained with chlortetracycline is not always accompanied by improvement of the radiological picture. The differential diagnosis of this abnormal small bowel pattern encountered in diabetics with or without steatorrhea includes pancreatic insufficiency, nontropical sprue, enteroenteric fistulas and Whipple's disease[16,55].

Mesenteric artery thrombosis with small intestinal gangrene is not common in diabetes. However, its incidence is somewhat increased, due to frequent occurrence of arteriovascular disease in diabetics[36]. The radiological findings of mesenteric thrombosis are those of intestinal obstruction, namely the presence of many distended loops of bowel filled with air and fluid.

DISORDERS OF THE LIVER AND BILIARY TRACT. Hepatomegaly occurs frequently in juvenile diabetics and, in adults, it is by no means uncommon[79]. Usually, the enlargement is due to fatty infiltration of the organ. On roentgenograms, the enlarged liver is frequently detected as a homogeneous density in the right upper quadrant, sometimes displacing the stomach or colon and small intestine.

Increased liver density beyond the normal appearance has been noted in several patients with hemochromato-

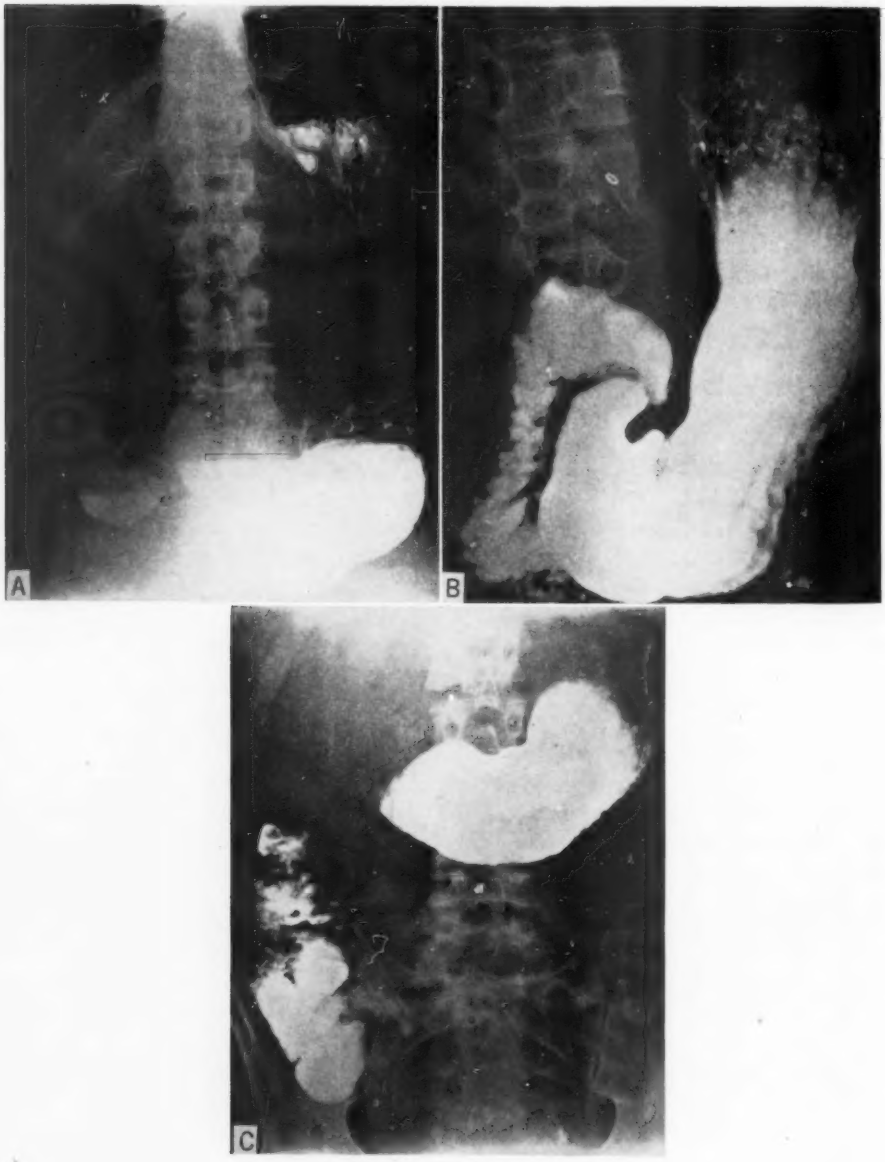

Fig. 3.—Visceral neuropathy in diabetes.

(*A*) Atonic stomach partially filled with barium in 27-year-old severe diabetic. Erect position, showing ptosis and fluid levels in stomach and descending duodenum.

(*B*) Stomach and duodenum in supine position. No signs of obstruction. Same patient as in (*A*).

(*C*) Considerable gastric retention after 24 hours (same patient as in [*A*] and [*B*]).

sis[162] but this observation has not been confirmed by other investigators. The incidence of primary carcinoma of the liver in hemochromatosis is high[85,165].

The prevalence of cholecystitis and cholelithiasis in diabetics has been demonstrated repeatedly[43,85,137,172,175,179]. The incidence ranges from 23%[43] to 35%[153,183] in contrast to 3%[181] to 21%[113] in the general population. Cholelithiasis in diabetes is often associated with arteriosclerosis, and suggests a common etiology in disordered fat metabolism. The biliary calculi are usually radiolucent and often contain cholesterol; sometimes, however, they contain chiefly pigment[179]. When cholecystitis is produced by gas-forming organisms such as *Escherichia coli* and *Clostridium welchii*, emphysema of the gallbladder wall or intraluminal gas may be detected on roentgenograms[13,47,167]. These findings are rarely observed, but they occur predominantly in diabetics. Extremely dense homogeneous gallstones, simulating a metallic density have been seen in hemochromatosis[30]. Nonvisualization of the gallbladder on oral cholecystography in diabetics can frequently be explained by a prolonged gastric retention of the contrast medium[89].

DISORDERS OF THE PANCREAS. In chronic pancreatitis, diabetes is a frequent occurrence. The chronic relapsing form is recognized radiologically by diffuse calcification which outlines the pancreas partially or completely, in the retrogastric space[10,108,152]. Acute exacerbations of chronic pancreatitis may produce functional alterations of the adjacent duodenal loop with mucosal edema, deformity and sometimes with widening of the descending duodenum. An isolated gas-distended loop of upper jejunum indicating localized paralytic ileus has been described as a roentgenographic sign of acute pancreatitis. This sign, however, is not completely reliable and is frequently not present. Pancreatic carcinoma is more frequent in diabetics. Fourteen per cent of all deaths due to malignancy in diabetes are due to pancreatic carcinoma, compared with an incidence of 2.5 to 5% in nondiabetics[85]. Cysts and pseudocysts of the pancreas may also be associated with diabetes. They frequently displace and deform the stomach, duodenum and colon, and infrequently show marginal calcification[130].

Lesions of the Genitourinary Tract. The urological lesions associated with diabetes mellitus have received considerable attention in the recent literature, chiefly because diabetic nephropathy has become a major cause of morbidity and mortality in the post-insulin era. Indeed, the postmortem incidence of upper urinary tract infection in diabetics is steadily increasing. In the period before 1945 approximately 20% of all diabetic deaths exhibited this finding; in the interval between 1950 to 1957, the incidence rose to 41%[85,148].

The metabolic deposition of glycogen or fat in the renal parenchyma, observed in diabetes, is not demonstrable radiologically. Kimmelstiel-Wilson's intercapillary glomerulosclerosis also produces no characteristic roentgenographic signs. However, intravenous urography frequently reveals poor visualization of the excretory system due to impaired renal function.

The diagnosis of acute pyelonephritis is made predominantly from clinical findings. Urograms usually show no abnormalities. Only occasionally, an incomplete filling or contraction of the renal pelvis and calyces, presumably due to spasm, may be observed.

Chronic pyelonephritis in diabetics is usually a bilateral infection. It is commoner in women and is usually caused by a mixture of *Escherichia*

coli, nonhemolytic streptococci and *Aerobacter aerogenes*. Radiologically, the earliest sign of the disease is blunting and irregularity of the minor calyces. Pyelocaliectasis occurs at a somewhat later stage. The surface of the mucosa of the renal pelvis and calyces becomes indistinct, contrasting to the more smooth outlines seen in obstructive hydronephrosis without infection. As the lesions progress, fibrosis and scarring may cause considerable distortion of the calyces. The ureters become dilated and tortuous and sometimes exhibit irregular segmental dilatation and constriction[21].

Necrotizing renal papillitis (renal papillary necrosis, renal medullary necrosis or papillitis necroticans) is a pathological entity which sometimes complicates infections of the urinary tract[48,50,63,64,70,129,144,170,173]. Its greatest frequency is in young diabetic women[5,63,70]. In a review of 194 cases, representing all reported cases before 1953, 61% had diabetes mellitus and 27% had obstructive urinary lesions[93]. Several factors, including arterial and arteriolar disease, bacterial toxicoses, and extrinsic pressure on papillary vessels from deposits of amyloid, edema, venostasis and pyelotubular reflux, promote necrosis in the presence of pyelonephritis[40,51]. Three forms of the disease have been recognized clinically: 1) an acute fulminating type which usually ends fatally in a few days or weeks, 2) a subacute type, which extends over several months, and 3) a chronic type, which extends over several years. When untreated with antibiotic therapy, the disease is almost always fatal. Pathologists have distinguished between medullary and papillary necrosis, depending upon the major site of the initial change.

Roentgenographically, slight enlargement of the renal shadows may be discernible in acute cases[129]. In the subacute and chronic types, both kidneys appear atrophic[93] and intravenous urograms frequently show a poor concentration of the contrast medium due to impaired renal function. Unilateral renal involvement is quite rare[93]. Retrograde pyelography is usually best able to demonstrate the intrarenal morphological changes. Early in the disease process, only the signs of pyelonephritis may be seen. As detachment and sequestration of the renal papillae occur, the contrast material may be seen extending into fine sinuses which form an arc and eventually a ring shadow in the necrotic region (Fig. 4*A*). With complete detachment, necrotic particles, floating freely in the calyces or renal pelvis appear as filling defects and mimic calculi or small tumors. If they enter a ureter, obstructive uropathy and renal colic may ensue. Usually several papillae are destroyed in each kidney. Calculus formation may occur around the necrotic fragments[96]; in one series, calculi were seen in 21 out of 55 cases[93].

In the early stages, renal papillary necrosis may be difficult, radiologically, to differentiate from renal tuberculosis. However, parenchymal calcifications, strictures of the calyceal infundibula and eventual widespread destruction of tuberculosis are not seen. In the differential diagnosis, other causes of bilateral renal atrophy must also be considered. The contrast-filled channels invading the papillae may be confused with the cavities of hypoplastic kidneys, or calyceal diverticula.

Gas-forming organisms occasionally are the cause of chronic infection of the urinary tract. In such instances pneumaturia may be present[45,54,122,127,128,142]. On abdominal Roentgen-ray films, this condition may produce a radiolucent halo of gas which outlines the renal shadow, also multiple small gas bubbles are frequently seen within

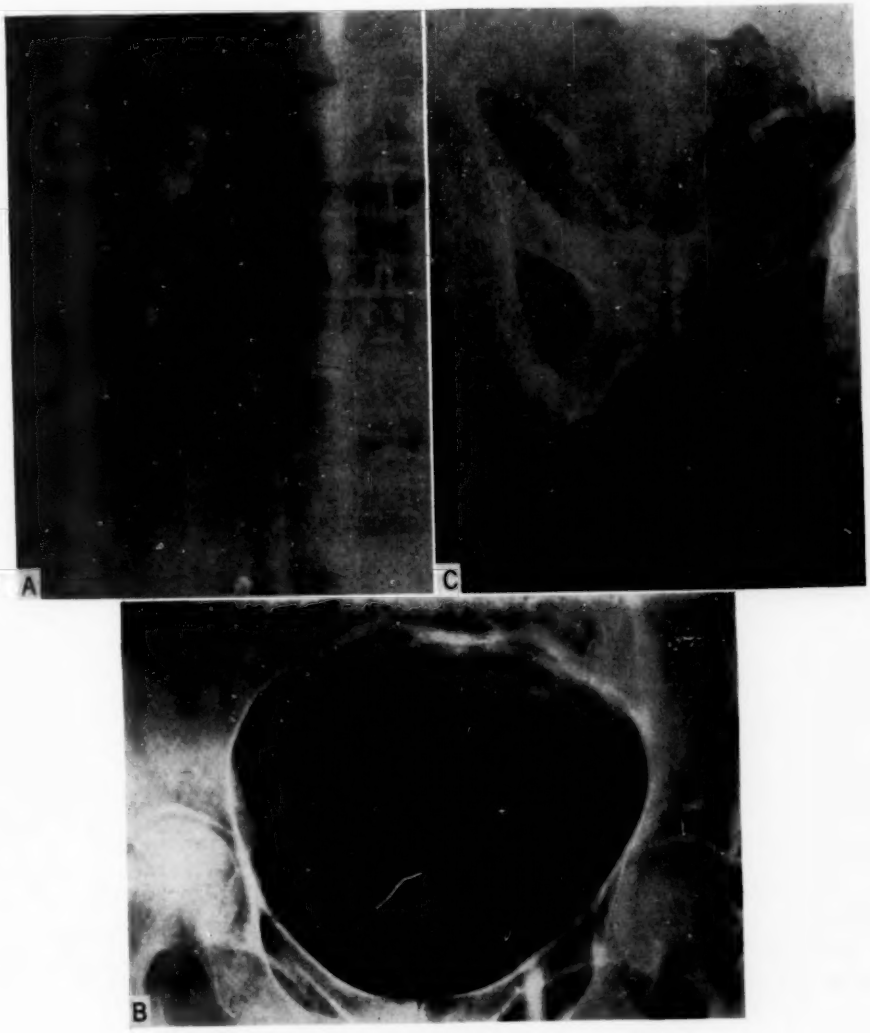

Fig. 4.—Changes of the genitourinary tract in diabetes.

(*A*) Retrograde pyelogram: Papillary necrosis involving entire kidney. Cavitation, arc and ring-shadows indicating total or partial detachment of papillae.

(*B*) Cystitis emphysematosa on plain film of pelvis. Broad concentric radiolucent ring of interstitial gas.

(*C*) Bilateral total calcification of vasa deferentia. Also calcified pelvic arteries.

the renal pelvis and calyces, and sometimes within the renal parenchyma[13,54,85]. Often, gas finds its way into the bladder wall. Multiple small vesicles may then be observed cystoscopically. This condition, called cystitis emphysematosa[19,38,41,53,54,67,122,128,142], produces a characteristic radiological picture. Concentric radiolucent rings silhouette the periphery of the bladder on plain films (Fig. 4*B*). Cystograms with contrast material distending the bladder to varying degrees confirm the location of the gas. The emphysema may subside when the thin-walled vesicles rupture into the bladder lumen during contraction[41].

Neurogenic bladder secondary to diabetic neuropathy has been observed in as high as 25% of diabetics with autonomic nerve involvement[83,84,109,149,150]. Chronic cystitis is a common sequel[85,109,150,164]. On roentgenograms, the large atonic bladder presents as a dense oval mass in the pelvis displacing the gas shadows of the small bowel and sigmoid colon. On urograms, reflux of contrast material into the dilated ureters is observed. These radiological changes are usually irreversible.

When bilateral calcification of the vas deferens is seen on roentgenographic films of the abdomen, the diagnosis of diabetes should be suggested. In one series of 60 cases, 56 were diabetic[85]. The calcification is thought to be due to arterial insufficiency[102]. Usually the posterior or ampullary portion of the vas is calcified. As the linear calcific shadow extends laterally, it usually curves downwards and then medially. Sometimes the entire vas is calcified, including the scrotal portion (Fig. 4*C*); the nature of the calcification is then obvious. Identification of the calcified vas is difficult only if a small segment is involved. Calcification of the seminal vesicles occurs relatively infrequently[25,52,76,81,185].

Concurrent Diseases of Diabetes Producing Roentgenographic Changes. PULMONARY LESIONS. (a) *Hyaline Membrane Disease.* Because this disease is prevalent in premature infants and those delivered by Caesarian section, its incidence is increased in the offspring of diabetic mothers. In one series, 16% of infants delivered by diabetic mothers[13] developed this lesion. Radiographically, the lungs usually appear normal at birth, but within a few hours, a fine miliary pattern appears. Sometimes the lungs show increased radiolucency, due to overdistention[115].

(b) *Tuberculosis.* According to Joslin, diabetic patients have a greatly increased susceptibility to tuberculosis, particularly during periods of poor control or diabetic coma[85]. The distribution of tuberculous lesions in the various organs is similar to that of non-diabetics[174]. In the pre-insulin era, active pulmonary tuberculosis was a rapidly progressive disease with a mortality rate of above 50%[152]. Following the use of insulin, the incidence of pulmonary tuberculosis in diabetics fell to one-third of the former incidence. Chemotherapy has further decreased the mortality rate, so that now it is only approximately twice that in non-diabetics[154].

(c) *Mucormycosis.* Mucormycosis, a usually fatal fungus infection which frequently involves the lungs[8,49], has been recognized with increasing frequency in recent years. Sixty-five per cent of these infections occur in diabetics. The pulmonary lesions also occur as a complication of leukemia and multiple myeloma, particularly during therapy with cytotoxic agents, antibiotics, or ACTH. Radiologically, the pulmonary findings are those of nonspecific segmental pneumonitis. Pleural reaction and abscess formation may occur.

LESIONS OF THE ORBITS, SINUSES AND

SKULL. In all types of cataract, the calcium content of the lens increases from the normal range of 9 to 17 mg. per gm. to a range of 20 to 200 mg. per gm.[176]. When the calcium content becomes sufficiently high, the cataract becomes visible radiologically. The senile type of cataract is frequently seen in diabetics, often at an earlier age than in nondiabetics. The "complicated" type of cataract secondary to other ocular lesions is not increased in incidence in diabetes[85]. The so-called "true diabetic" cataract which develops rapidly in young diabetics is rarely seen.

Radiologically, the calcified lens appears as a circular density (Fig. 5*A*). Sometimes the shadow is broken into two semicircles. The diameter of the lens does not exceed 7 mm.[171], so that the cataract is readily distinguished

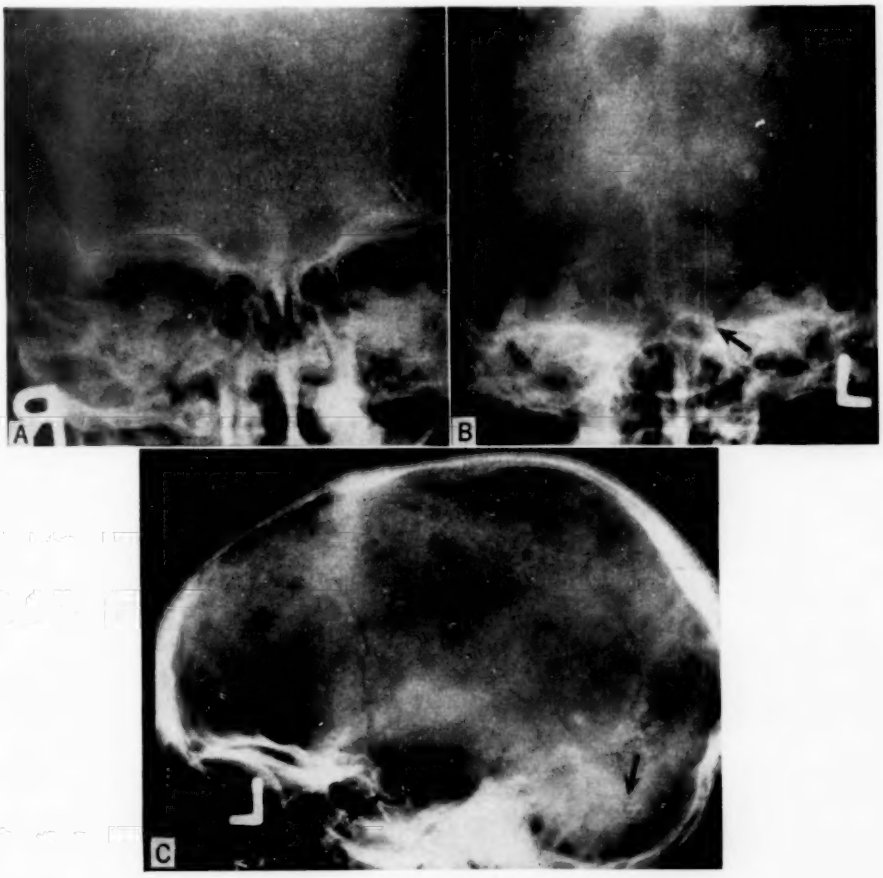

Fig. 5.—Intracranial calcifications observed in diabetes.

(*A*) PA film of skull. Calcified lens in cataract of right eye.
(*B*) and (*C*) AP and lateral films of skull. Curvilinear dense striations in calcified dentate nuclei (upper arrows). Also bilateral calcification of internal carotid arteries (lower arrows). (Same patient as in A.)

from the larger crescentic marginal calcifications of the choroid, or from irregular calcifications of the vitreous.

Cerebral calcifications in diabetes mellitus have not been reported. An instance of bilateral calcification of the dentate nucleus in a diabetic woman is demonstrated in Fig. 5*B* and *C*.

may also occur with acidosis from other causes, generalized cachexia, cirrhosis, and as a complication of steroid or antibiotic therapy. The radiological findings include clouding of the sinuses and thickening of their mucous membrane. Air-fluid levels are not usually seen. Although these findings are non-

Fig. 6.—Lipo-hypertrophy in soft tissues of upper arm following periodic insulin injections.

These curvilinear dense striations have previously been observed in patients with Paget's Disease[88] and tuberous sclerosis[77].

In mucor fungus infections, the paranasal sinuses are usually involved at an early stage, before the lungs and central nervous system are affected[61, 92,161]. The infection may occur in diabetics, particularly with acidosis, but

specific, the diagnosis should be suspected if these changes occur in a toxic diabetic patient with swelling or cellulitis of the facial, peri-orbital and nasal tissues, and with black necrosis of the turbinates.

LESIONS OF THE SOFT TISSUES OF THE EXTREMITIES. Among the various skin manifestations encountered in diabetes, only a few can be demonstrated radio-

TABLE 1.—SUMMARY OF RADIOLOGICAL MANIFESTATIONS OF DIABETES MELLITUS

	Calcifications, usually degenerative	*Infection*	*Neurogenic*	*Juvenile*	*Other*
Extremities	Arterial { atheromatosis medial necrosis	Gangrene & osteomyelitis of feet	"Pseudotabetic" joints in lower extremities	Mauriac's dwarfism (open epiphyses & osteoporosis)	Lipodystrophy due to insulin injections. Increased incidence gout
Gastrointestinal	Cholelithiasis Pancreatic	Cholecystitis Emphysematous gallbladder	Visceral neuropathy	Hepatomegaly	Gastric atony & retention and impaired motor function of small bowel in acidosis. Increased incidence pancreatic carcinoma.
Genitourinary	Vas deferens	Chronic pyelonephritis Renal gas-forming infections. Cystitis emphysematosa	Neurogenic bladder		Renal papillary necrosis
Skull	Arterial Cataracts	Mucormycosis of sinuses & orbits			
Lungs		Mucormycosis Tuberculosis			Hyaline membrane disease in offspring.

logically. Most soft tissue structures have a density equivalent to that of water and hence are indistinguishable from one another in the radiographs. Areas of lesser density, due to gas formation or fatty tissue, and areas of increased density due to calcium deposits are distinguishable. The radiolucent streaks of gas sometimes seen in diabetic gangrene have been mentioned previously.

Abnormal radiolucent areas between muscles and in subcutaneous tissues of the deltoid and gluteal regions are not infrequently seen in Roentgen-ray films of diabetics (Fig. 6). This localized "lipodystrophy" is secondary to repeated injections of insulin[3,6,14,101,134]. The lesions are quite distinct from the nonspecific granulomas which may develop after any series of subcutaneous injections. The localized metabolic disturbance with deposition of fat is initiated directly by the injected insulin, and has been produced experimentally[85]. The affected extremity may become either atrophic or hypertrophic. In one series of 1,096 unselected diabetics, some degree of atrophy was demonstrated in 24% and in patients under 20 years, in 44%[85]. Both the atrophic and hypertrophic lesions are seen more commonly in juvenile diabetics[57]. On roentgenographic examination, the radiolucent lipomatous tissue may appear either lobulated, homogeneous and sharply defined, or dispersed through the muscular and connective tissues.

A very rare observation is the deposition of calcium in the corium of the skin in diabetic patients, reported by Root[148]. Its cause is not known.

Discussion. From the foregoing review it will be apparent that only a few of the many Roentgen-ray findings described in diabetes are characteristic, such as calcification of the vas deferens and cystitis emphysematosa. The important role of diagnostic roentgenology in this disease is therefore not in the primary diagnosis, but in the detection and evaluation of the many complications which may occur. Of particular importance is the use of films of the lower extremities and of arteriography in the evaluation of vascular insufficiency and in the detection of osteomyelitis. Urography is a most important adjunct in the study of diabetic urinary tract infections.

A summary of the more important radiological manifestations is given in Table 1. Here, the lesions which are caused by infection, degeneration, and neuropathy are listed according to their effect on various structures. The radiological changes attributable to infection alone are numerous.

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THERAPEUTICS

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CURRENT MANAGEMENT OF THE PATHOPHYSIOLOGICAL DISORDERS IN CIRRHOSIS AND HEPATITIS

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DESPITE the availability of newer procedures for the study of hepatic disease, therapeutic measures designed to affect the function of individual hepatic cells have not been forthcoming. The eventual return of function of hepatic tissue in acute processes is dependent upon removal of the injurious agent and the general support of the patient until some degree of stability is restored. While this is also true of more chronic stages of liver injury, the development of physiological and clinical abnormalities in the cirrhotic can be related to the degree of function of the regenerating nodules, whether small[62] or large[71,72] which substitute for dying parenchymal liver tissue in the midst of fibrous replacement, cellular exudate, and biliary hyperplasia. In those instances where injured hepatic parenchymal tissue has not been replaced by adequately functioning regenerating cells sufficient to maintain normal metabolic requirements, then varying clinical abnormalities will occur despite the fact that the latter cannot always be correlated with the morphologic picture[89]. It is of interest that an organ which is involved in the numerous functions that have been ascribed to the liver may carry on certain processes satisfactorily, but be partially or totally deficient with respect to others. As a result it is not uncommon to find specific therapeutic problems concerned with fluid retention, ammonia intoxication, jaundice, gastrointestinal or constitutional symptoms, individually or combined in any given patient. In addition, alterations in the portal vein-hepatic artery relationships which occur within the changing hepatic tissue may give rise to portal hypertension, collateral circulatory abnormalities and acute hemorrhagic episodes which further complicate the problem. Also the presence of portal hypertension and splenomegaly have been associated with hematologic disorders which are well recognized.

The purpose of this paper is to re-

view some of the current concepts concerning the basic physiologic abnormalities occurring in this disease and outline the present trends in their management.

ETIOLOGIC CONCEPTS. Because of the enormous reparative power of hepatic tissue permanent damage may take place over variably long periods of time only after repeated subclinical insults in the insidious cases, or after moderate to overwhelming injury in the more obvious instances. The relationship between alcohol consumption and nutritional deficiency has long been recognized and would more commonly be identified with the gradual development of hepatic injury. Hoffman *et al.*[48] have shown in rats that injured liver cells, even after repair and return to histologic normality, do not respond to a second injury as do normal cells. Some question still exists as to whether or not alcohol has a specific effect in the production of hepatic injury or whether it is the accompanying inadequate diet alone which causes damage[56]. Many workers do not feel, however, that a toxic effect is important. Of interest, is the report of Best and co-workers[12,13] in which they described that a nutritionally deficient diet produced no disease in rats until alcohol was added. Cirrhosis then developed. Realizing that the control diet and the same diet plus alcohol were not isocaloric, sucrose was substituted for alcohol. Again cirrhosis developed. From this it has been suggested that a caloric factor is related to hepatic injury in the presence of dietary deficiencies. Klatskin[56] and others[12,13] have pointed out that the alcoholic may consume a normal quantity of calories per day, but in the presence of deficient protein consumption, liver injury may occur. It has been postulated that choline requirements vary with the total caloric intake, increasing as the calories increase[56]. This might explain the lack of nutritional cirrhosis in pure starvation states[103]. Other speculation suggests that oxidation of excess calories in the absence of adequate protein may occur via abnormal metabolic pathways with fatty deposition of the liver occurring as an intermediary of these pathways, or with the formation of toxic end products harmful to normal hepatic tissue, or with exhaustion of enzymatic functions because of depletion of basic building blocks. The latter is of note in view of the demonstrated zinc deficiencies in alcoholics with cirrhosis reported by Vallee and co-workers[117,118,119].

Studies relating choline metabolism to experimental fatty cirrhosis were an outgrowth of the discovery of insulin[12]. Pancreatectomized dogs receiving extracts of insulin soon developed fatty livers probably because they lacked pancreatic enzymes[48] required to remove choline[14] from their diets. These animals and others[15] eventually developed cirrhosis[20], the pathways for which have been well outlined[46]. Arguments have been offered, however, that these animal studies are not applicable to man and that fatty deposition in man as such does not produce cirrhosis[121]. More recently Wilgram has produced a Laennec's type of cirrhosis in monkeys using a diet low in protein, free of choline, and rich in cholesterol. That autoimmune phenomena may develop against liver cell protein altered by injury was suggested as a possible perpetuating phenomenon after removal of all injurious factors[123].

Experimental liver injury may also be produced by diets deficient in sulfur containing amino acids (cystine) and vitamin E[1,2,42]. In these instances a necrogenic effect on liver cells is obtained in contradistinction to the fatty infiltration seen with choline deficient

diets. Antibiotics given orally[41] which produce changes in the intestinal flora[99] have an inhibitory effect on the development of necrotic lesions. The end results of this injury are similar to toxic or post-necrotic cirrhosis seen in man, but in the latter the etiology is not always clear-cut[105]. Dispute exists as to whether or not viral hepatitis in man is a frequent factor in the development of this type of hepatic injury. Several well-documented reports of viral hepatitis which progressed to post-necrotic cirrhosis are now recorded in man[6,29,57,58,61,67], and in some studies the presence of a previous history suggesting hepatitis has been offered as a possible basis for viral etiology of cases of cirrhosis occurring in non-alcoholics without deficient dietary histories[10]. A report comparing cirrhosis in Boston and cirrhosis in England emphasizes these differences in etiology[109]. Further studies of different types of dietary deficiencies in Uganda and Jamaica are recorded as possible factors in the eventual production of a cirrhotic-type picture[12,28].

The ever increasing list of drugs[40] which produce hepatic injury is not thought to be a major factor in the development of cirrhosis, for though isolated instances of permanent or fatal disease can be found, the vast majority of drugs usually result in disease which is transient and often cholestatic in nature. A detailed review of drug-induced liver damage was presented recently by Popper and Schaffner[87].

Awareness of Wilson's disease and its relation to copper metabolism[54] and the associated development of cirrhosis[9] has been emphasized, and one instance of cirrhosis following hepatitis of infectious mononucleosis[65] has been recorded, although studies indicating normal hepatic function prior to the attack of infectious mononucleosis were not available. Diabetes, ulcerative colitis and regional ileitis have also been associated with the development of cirrhosis. The relationship between these illnesses and cirrhosis is not apparent, except that fatty deposition of the liver is more frequent in diabetics who have had episodes of ketosis and in these instances fibrotic changes occur more frequently[52,93].

A severe progressive insidious cirrhosis of the post-necrotic type has been reported in young girls and women characterized by endocrine abnormalities, arthralgias, and hypergammaglobulinemia. The possibility that this is a variant of viral hepatitis has been suggested[10].

ACTIVE LIVER DISEASE. Because subacute hepatic necrosis may occur insidiously[57], the opportunity to treat patients may not present itself until some phase of hepatic decompensation occurs. In the case of alcoholics, adequate diet and abstinence will frequently effect a remission or cure even after moderate abnormalities have been produced[86]. In the non-alcoholic, however, where the etiology is not as clear, the process may not be easily reversed. Bed rest and proper diet are the mainstays of therapy.

The efficacy of *bed rest*[34,45,113] is not only a clinically observed fact, but also a sound physiological adjuvant to healing. Blood supply to the liver is decreased in the upright position and further reduced following exercise[18]. In acute hepatitis, however, studies have shown that once the serum bilirubin falls below a level of 2.0 to 3.0 mg. per 100 ml., strict bed rest will not hasten recovery[111]. In these instances gradual activity can be begun and if relapse, which is uncommon, does not occur further activity may be permitted. Bromsulfalein retention and bilirubin levels should be followed at weekly intervals using improvement in

these tests as a guide to increasing activity[45]. Similarly, in chronic hepatic disease bed rest or modified activity is desirable until some form of stability occurs both clinically and chemically.

In all of these instances a high protein diet[22,34,45,111,113] is most efficacious unless ammonia intoxication is present. (See below.) Controlled studies on Servicemen[21,23,111] with infectious hepatitis in Germany and Japan have shown that 3,000 calorie diets with 150 to 190 gm. of protein produced the best results. No limitation of fat is required and choline supplements are not needed. Multivitamin therapy has been recommended though it is probably nonspecific. A similar regimen should be instituted in chronic liver disease and maintained as long as improvement continues.

During the early stages of acute hepatitis, anorexia, nausea and vomiting may interfere with dietotherapy. In these cases intravenous infusions of 1000 to 2000 ml. of 5% dextrose in water are recommended[44]. Usually after 24 to 48 hours oral intake can be started. Additional therapy in more severe cases which do not respond to such conservative management is considered separately with regard to use of steroids and development of coma.

In the alcoholic other more specific nutritional deficiencies are not uncommon, and include multiple or single deficiencies in the vitamin B group and vitamin C. Davidson[26] has recommended that all alcoholics be given ample amounts of vitamins B and C, though once maintained on a nutritious diet, supplementation may not be as necessary.

Popper *et al.*[88,89] and others[86] have called attention to the acute hepatic steatosis occurring in alcoholics associated with parenchymal cell necrosis, polymorphonuclear infiltration, Mallory bodies[71] (hyaline, degenerative lesions), and a severe, often fatal, active, hepatocellular disease. This "florid" lesion does not always respond to nutritional therapy as compared with the simple fatty liver which most frequently improves with good diet in 2 to 3 weeks. The nature of the Mallory lesion and the peculiarly severe disease in this group of patients have not been thoroughly studied with respect to their relationship with other forms of malnutrition[27]. Some observers dispute whether or not the hyaline degeneration seen in livers of alcoholics is a specific lesion. One group feels that it has prognostic importance in the overall outlook of such patients, in that more severe disease can be correlated with more frequent hyaline degeneration seen on biopsy[96].

Non-inflammatory hyperplasia of the parotid gland has been noted not only in alcoholic cirrhosis, but also in starvation states. The exact nature is unknown, but similar to nutritional deficiency, improvement is often seen with concomitant improvement in the liver disease[19,97,123].

The severe cirrhotic suffering from prolonged anorexia or vomiting often presents a serious problem in dietary management. Tube feedings using milk and dextro-maltose[27] have been recommended since intravenous fluids over prolonged periods can hardly supply the needed protein and caloric requirements.

Specific dietary problems will be found in individual patients. In the presence of protein toxicity the latter may have to be specifically limited. This will be discussed more fully in relation to ammonia intoxication and hepatic coma. In patients with fluid retention with or without ascites, limitation of sodium to 200 to 500 mg. per day may be required. In instances where steatorrhea is present, possibly due to associated pancreatic disease in

the alcoholic, supplementary pancreatic enzymes (pancreatin)[27] have been suggested.

The presence of jaundice is not generally a problem unless some form of cholestasis of bile occurs. In these instances pruritus may be disturbing and often not responsive to antihistamines, mild sedation, intravenous procaine and ergotamine, though the use of starch baths may be temporarily effective. Methyl testosterone orally must be used advisedly since it is an occasional cause of intrahepatic cholestasis[3]. The mechanism of its effectiveness is not known. Relief of obstructive phases of disease is often associated with improvement. The latter may be the explanation for improvement of pruritus following steroids[45].

Anemias are not an uncommon accompaniment of hepatic disease. Macrocytic or occasionally megaloblastic anemias have been found which responded to daily doses of 250 to 1500 μg. of folic acid administration[53]. Normocytic anemias may be due to hemodilution[36], diminution of formation[26] or increased destruction of red blood cells. The latter is most often seen in patients with portal hypertension and splenomegaly where it is postulated that sequestration of cells[33] may occur with further destruction of circulating cells by immune phenomena or by inhibition of bone marrow production[26]. Neutropenia and thrombocytopenia may be present and can be treated by supportive measures including transfusions and steroids which are not always satisfactory. Consideration for splenectomy depends upon the severity of the disorder and the feasibility of surgery.

Blood loss anemias are a common complication in patients with cirrhosis. Vitamin K therapy may be useful when hypoprothrombinemia is present. Iron therapy and transfusion may be additional agents. Care should be exercised to prevent overzealous use of blood in those instances where blood loss is not the cause of anemia, or where the hemoglobin is above 10 to 11 gm.

The prevention of acute hepatitis in individuals exposed to active disease has been noted following prophylactic administration of gamma globulin. The administration of 0.06 ml. of gamma globulin per pound of body weight reduced the incidence of hepatitis to 1.7 per 1000 in inoculated persons as compared to 22.5 per 1000 for controls[118].

ADRENAL STEROID THERAPY. The usefulness of adrenal steroids in patients with liver disease has received considerable attention[45,102]. In the average case of hepatitis it is agreed that the steroid hormones offer no advantages because of the close resemblance to controls and the frequent relapses following drug withdrawal. Generally, more rapid clearing of jaundice, return of appetite, greater food consumption, and increased weight gain have been recognized following institution of the drug[50]. Nelson[79] has recommended its use, however, in patients only when the serum bilirubin is greater than 15 mg. per 100 ml., when anorexia, nausea or vomiting cannot be controlled or when hepatic necrosis is marked as evidenced by shrinking liver, coma, fetor or disturbed sensorium.

In these instances Sborov *et al.*[102] have given 20 mg. ACTH intravenously slowly over 8 to 12 hours for 5 days with subsequent reduction in dose as the bilirubin fell. Other workers have used prednisone[44] in doses starting with 75 mg. daily because of lesser effects of sodium retention.

Some observers have noted improvement in selected cirrhotics[47,91,100,119] following institution of steroid therapy, but whether this is the result of a direct, beneficial effect upon the liver,

or due to nonspecific changes in appetite, food intake, and well-being is not known. Rise in serum albumin and drop in serum bilirubin have been noted[17]. The rapidity with which serum bilirubin may fall following treatment in hepatitis has suggested a choleretic effect of the drug[83], but conflicting experimental studies are reported[24,104]. Chronic hepatitis progressing to postnecrotic cirrhosis treated over long periods has shown reversion to quiescent disease with large areas of scarring not infrequently found on biopsy. That such cases would not have developed similar outcomes without steroidal therapy cannot be stated because of difficulty in controlling studies. Improvement of clinical status soon after institution of the hormone in cases having prior treatment with diet and rest has occasionally been impressive[29,91]. The long term outcome in these individuals, however, is still uncertain. The reasons why some patients respond and others do not are also nebulous. Care must also be exercised in that fluid retention, diabetes, hypertension, potassium depletion, peptic ulceration and bleeding may be important complications of therapy. Davis *et al.*[29] noted rise in portal pressure in a patient with chronic hepatitis following a course of ACTH therapy. Whether ACTH effected changes in intrahepatic scarring and regeneration of liver tissue thus influencing intrahepatic vasculature, or whether this was natural complication of the disease is unknown.

As yet no general recommendations have been made in cirrhotics with regard to selection for long term therapy with steroids. A trial of the drug may be considered if progression of disease or poor response has occurred after an adequate period of observation on rest and nutritious diet. Efficacy of these drugs in treatment of hypersplenic disorders has been disappointing. The use of these hormones in ascites and hepatic comas will be considered below.

PORTAL HYPERTENSION AND BLEEDING VARICES. The application of newer techniques for the study of patients with cirrhosis has resulted in a greater awareness of the variations which may occur from one patient to another. That portal hypertension may be found in asymptomatic patients with minimal biochemical abnormalities, as well as in those with advanced disease, is recognized by the fact that patients are seen with acute variceal hemorrhage without previous history or symptoms of hepatic disease. Intrasplenic pulp measurements[4,30,92] occluded hepatic vein catheterization studies[59,95], direct manometric mensuration of esophageal varices during esophagoscopy[80] and direct needling of the portal vein[16], have resulted in reports attempting to evaluate the pathogenesis and ultimate prognosis and management of patients with portal hypertension. Catheterization and splenic puncture have gained widest acceptance, the latter often being accompanied by roentgenographic studies since intrasplenic instillation of radiopaque dyes radiographically outlines the portal vein and its collateral circulation (splenoportography)[64,76,114].

Besides being an aid to improved diagnosis, pressure measurements have shown that acute disease (viral hepatitis or severe fatty infiltration) may produce some elevation of portal pressure though usually not to the degree seen in cirrhosis. Following treatment with associated improvement of the liver, portal pressure may return to normal levels[64,92]. In patients with more advanced disease, such changes are less likely to occur with improved status probably because of more permanent intrahepatic vascular changes, unless natural collateral channels develop

and decompress the portal tree. The above mentioned development of acute variceal bleeding in previously asymptomatic patients points out the need for further study of this problem since the pressure level in the portal radicals may not be the prime factor which initiates the bleeding episode.

The chief problem of detecting nonbleeding varices and diagnosing their rupture in the case of acute gastrointestinal hemorrhage remains paramount in the management of cirrhosis although there is documentation of cases in which portal hypertension appeared in the absence of intra- or extrahepatic venous obstruction[112]. The above mentioned procedures have been utilized in diagnosing the presence of portal hypertension when barium swallow, too often not satisfactory[82], has been negative for varices. The use of esophagoscopy is often valuable in this respect. The presence of an elevated blood level of ammonia[75] and increased Bromsulfalein retention may be an additional diagnostic aid during hemorrhage[8].

Compilation of pressure studies has not been helpful in determining which patients are going to bleed in advance of a hemorrhagic episode[59,95]. The possibility that peptic acid erosion might be a factor has led to the suggestion that ulcer-type management may be effective in preventing bleeding[64], but sparsely available data of gastric acid and uropepsin secretions have not always indicated high levels in these patients[68,91].

Decompression of the portal vein whether by portacaval or splenorenal anastomosis appears to be advocated most often in the therapeutic approach to patients with a previous history of bleeding. Statistical studies tend to favor the former as the procedure of choice[88]. Dispute exists, however, as to whether or not the acute bleeding episode which does not respond to medical management should be subjected to immediate ligation of the varices or whether an emergency shunting operation should be performed[64,66,68,98,120]. Studies of the natural history of bleeding varices with regard to statistical outcome without surgery, have raised the question as to the value of shunting procedures, since it has been suggested that the prognosis remains minimally altered when one considers the overall picture in nonoperated cases[7,77]. It remains at present, that in carefully selected cases with adequate liver function, shunting operations may prolong life and decrease morbidity.

Institution of prophylactic shunt surgery prior to bleeding is not usually recommended since adequate tests are not available which can be used to predict which patients will bleed and which patients will not. The choice as to splenorenal, end to side, or side to side portacaval shunts is not solved[64]. Omentopexy, hepatopexy, ligation of splenic or hepatic arteries are generally not advocated. Splenectomy may be combined with splenorenal shunts, but by itself has little to offer except perhaps in those instances of hypersplenism (see above) in which hematologic abnormalities require efforts at correction:

The definitive management of the acute bleeding episode is concerned with blood replacement, prevention and treatment of shock, and control of the bleeding. Adequate intravenous therapy with plasma or plasma expanders is at most only a temporary adjuvant and must be replaced by fresh whole blood given in sufficient quantities to overcome the loss and treat shock. Precipitation of hepatic decompensation is not infrequent in such instances, and may be partly related to hepatic anoxia. Oxygen is a helpful addition, therefore. The proper and immediate

use of tamponade techniques using balloon tubes[25], has been well described and should be instituted early. The administration of saline cathartics to purge the intestinal tract of blood may be helpful in preventing absorption of nitrogenous wastes which could precipitate coma. Oral administration of neomycin may also be helpful in this regard, and is discussed below.

Evidence of continued blood loss despite institution of these techniques precipitates the consideration for surgical intervention as described above. Even in the best of hands the mortality remains high, however. For these reasons the search for simplified methods of controlling bleeding continues. Physiologic dynamic studies have revealed that intravenous surgical pituitrin decreases portal pressure and hepatic blood flow probably by pooling of blood in the splanchnic circulation[31]. Clinical trials in cases of bleeding varices have reportedly been successful in controlling bleeding even though intravenous administration of 20 clinical units of surgical pituitrin in 100 to 250 ml. of 5% dextrose in H_2O lasts for one-half hour[102]. If drop in portal pressure and decrease in collateral blood flow are efficacious in permitting clot formation, then even for short periods, the administration of this agent may prove to be worthwhile. Continued search for simple, but longer acting pharmacologic agents should be stimulated. Sufficient studies have not been performed to permit satisfactory evaluation. Care should be taken to determine if pituitrin may enable the patient to overcome the acute episode so as to permit evaluation for shunting at a later date.

ASCITES. Injection studies of postmortem specimens have shown that cases of cirrhosis with ascites appear to develop obstructive changes in the vascular outflow tracts of the liver[70]. In experimental animals obstruction of the hepatic vein results in an outpouring of hepatic lymph from all surfaces of the liver[51]. Pathologic sections of hilar areas from patients dying with cirrhosis have shown increased lymphatic channels in cases where ascites was present compared to cirrhotics without ascites[5]. Though portal pressure is generally increased in patients with ascites, portal hypertension is often present without fluid retention and portal pressures have occasionally been recorded in normal or minimally elevated ranges despite ascites[59,91]. Ascites has been noted without hypoalbuminemia, which, when present, must contribute to its formation. Excess loss of lymph which is high in protein, may be one of the mechanisms for the loss of albumin. Hyperaldosteronism has been a frequent finding in these cases, but by itself does not explain the variable development of fluid retention in cirrhosis. Theoretical mechanisms by which hyperaldosteronism develops may be related to decreased effective circulating blood volume as a result of splanchnic pooling occurring because of portal hypertension[55,64].

The management of a patient with fluid retention begins with restriction of dietary sodium. Not infrequently the simple restriction of intake to 200 to 500 mg. of Na per day may result in complete control of ascites. Care must be taken to continue adequate nutriments in these instances. The use of diuretics is also efficacious and the thiazide derivatives have been helpful in this respect. Doses of chlorothiazide (Diuril) vary from 0.5 to 2.0 gm. per day[69,90,101]. Care must be exercised with the latter, however, to prevent potassium loss which may precipitate further hepatic decompensation or neuropsychiatric changes[69,90]. The combined use of the thiazide drugs and mercurials can induce hyponatremia

and hypokalemia which can be quite troublesome and require separate electrolyte replacement therapy. Generally, the more refractory cases should be permitted long periods of treatment since correction of structural and biochemical abnormalities following dietotherapy may be the basic requirements before adequate diuretic response will occur.

Frequent paracenteses are not advisable because of large loss of body protein which is often difficult to replace. The use of salt poor serum albumin is costly and when effective may last only for transient periods.

Recently the use of anti-aldosterone drugs, such as Amphenone, has been tried, but the results have been inconsistent and variable and sometimes associated with neurologic disturbances clinically indistinguishable from coma[108,122]. Administration of the spirolactones, which appear safe to use, or of prednisone have been reported to effect a diuresis in refractory cases when combined with mercurials, where the latter have failed when used alone[39]. It is possible that the sodium-retaining effects of prednisone may be negated by an aldosterone inhibitory effect which then permits response to mercurial administration. Spiranolactone (aldactone) has been given in doses of 300 to 600 mg. per day followed on the second or third day by a mercurial injection with effective diuresis and dry weight occurring after variable periods of time.

The relationship between adrenal hormones and fluid retention has been further emphasized by the beneficial effect of bilateral adrenalectomy in a patient with massive ascites when sodium restriction was continued[38]. Portacaval shunts have also been reported to be effective in promoting diuresis and McDermott[73] has performed a "double" shunt procedure anastomosing both the hepatic and splanchnic ends of the portal vein to the vena cava with successful results. These procedures, however, are formidable and adequate studies are not available to outline their usefulness.

HEPATIC COMA AND AMMONIA INTOXICATION. The development of portal hypertension results in the eventual attempt by the body to decompress the portal system. The opening of extrahepatic venous collaterals is Nature's way of producing a spontaneous reduction of the elevated pressure. Although this is not usually effective in reducing portal pressure, measurements have been recorded in patients which are only mildly elevated and which are associated with large venous shunts[114]. The development of this collateral circulation opens up new avenues through which blood returning from the gastrointestinal tract may bypass the liver and unload toxic substances derived from alimentary sources into the general circulation. The detoxifying abilities of the liver are thus ineffective in removing noxious substances from the general circulation. Vascular shunts are an important cause, therefore, for the development of intoxications associated with hepatic failure. Inability of hepatic cells to detoxify these substances is another factor more commonly associated with severe cellular necrosis or decompensation.

In early experiments with Eck fistula dogs it was recognized that administration of protein produced a deleterious effect[43]. More recently numerous experiments have shown a relationship between blood ammonia and coma[107] although this relationship is not always clearcut. In the mammalian organism the production of ammonia is the result of enzymatic action of bacteria in the presence of nitrogenous products[85]. Many cases, however, have failed to show a correlation between venous

ammonia levels and symptoms[106]. The fact that peripheral muscles remove about 50% of blood ammonia has been suggested as an explanation of the latter since chemical determination of venous blood ammonia could mask arterial bathing of the brain. The chemical mechanisms for the production of coma by ammonia may be another cause for the discrepancy between blood levels and clinical status. Depletion of intermediate steps in the Krebs cycle by excess blood ammonia has been postulated as interfering with normal brain reactions and possible utilization by the brain of ammonia itself in other reactions. Thus a patient with only mildly increased ammonia levels over long periods of time could deplete oxidative reactions and interfere with cerebral metabolism in a manner similar to the effect of higher levels of blood ammonia over shorter periods of time[11].

These theoretical considerations have suggested two types of coma[35]. The first may be precipitated by administration of exogenous ammonium salts or protein as blood from hemorrhage, and is associated with high blood ammonia which may respond to glutamate therapy. The second type occurs spontaneously during progressive hepatic failure and may be related to decrease in hepatic mechanisms for detoxification through urea synthesis. Both of these should be differentiated from electrolytic depletion (particularly of potassium) which can mimic the clinical findings of tremor (flapping) and disturbed sensorium. The presence of fetor and elevated ammonia levels may also occur.

The treatment of patients with impending coma or coma is related to removal of substances concerned with the formation of ammonia or interfering with toxicity of ammonia already present. With respect to the former certain prophylactic considerations should be foremost in mind when treating patients with advanced hepatic disease. Ammonium compounds, narcotics, barbiturates should be used with caution for fear of precipitating toxicity. Frequent paracenteses, diarrhea, and diuretic administration have already been mentioned with regard to electrolytic imbalance. Acute gastrointestinal bleeding, introducing nitrogenous wastes into the intestines, can often precipitate toxicity, and in these instances attempts at purges are indicated to cleanse the gut.

The removal of all nitrogenous substances from the intestine regardless of the causative factors is the first step in combating this complication. All dietary protein must be stopped, and an intake of 1600 calories of dextrose should be instituted. As recovery begins, protein may be added to the feeding schedule, in 20-gm. increments at first on alternate and later succeeding days. Any relapse should cause a return to the previous program. In more chronic cases some form of permanent protein restriction may be required with variations between 40 to 80 gm. per day. Further administration may result in return of symptoms. In acute instances particularly those of exogenous etiology it is often possible to return to a normal diet. It appears that nitrogenous equilibrium in severe instances can be maintained despite low protein intake[106].

The concomitant administration of antibiotics appears reasonable in order to decrease intestinal bacterial action. Neomycin[37] appears to be the drug of choice since other broad spectrum antibiotics may produce diarrhea or staphylococcic enterocolitis, particularly after prolonged use. Administration of 6.0 gm. of neomycin a day orally in divided doses is given in acute cases, but 4.0 gm. of neomycin may be

effective in more chronic cases. Recent studies reporting renal and auditory toxicity of neomycin suggest that dosage adjustment or even cessation may be required occasionally[60,63].

Purgation in cases of hemorrhage has been mentioned, and some attempts should be made to allow normal free bowel activity. A saline cathartic has been effectively used. Return of coma and remissions have been correlated with constipation and drastic purgation respectively[32].

The rationale of glutamic acid therapy is based upon the combination of sodium glutamate with ammonia to form glutamine which transports ammonia to the kidney and by transamination with pyruvic acid to form alpha-ketoglutaric acid. Since glutamine does not pass the brain barrier, this reaction does not occur within the brain[11]. Variable results in therapy have been reported, using 25 to 50 gm. daily intravenously, and after initial enthusiasm, controlled studies have not indicated results which are superior to protein restriction and antibiotic therapy described above[110], although recommendation for use with beneficial results in acute cases has been made[35,74].

Arginine[78], ornithine and other comparable substances[106], have also been recommended because of their activity in the urea cycle. Again the results have not been uniform and are not recommended for routine use[106].

Massive doses of steroids have recently been reported to effect a remission from coma. As much as 250 mg., q.i.d., has been used for short periods[84]. In acute hepatitis with coma due to extensive necrosis their use may be of value. Sherlock recommends intravenous hydrocortisone in doses of 100 mg. every 6 hours[105]. In more chronic disease favorable results could be due conceivably to institution of other measures already mentioned.

Summary. The development of cirrhosis in man may result from a variety of causes many of which are poorly understood. The ultimate clinical picture may be similar regardless of the etiology and in any given patient it may be difficult to reconstruct the factors which are causing disease. Experimental studies related to nutritional aspects of hepatic injury have been reviewed and a brief correlation with disease in man is attempted. The relation of nutrition, alcohol, and viral hepatitis to the development of cirrhosis is discussed. The management of various phases of active liver disease with regard to diet, rest and drugs is outlined.

The physiological abnormalities attendant to end-stage liver disease have also been reviewed with emphasis on portal hypertension, ascites and hepatic coma. The current recommendations for management of these complications have been outlined.

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BOOK REVIEWS AND NOTICES

PERSPECTIVES IN VIROLOGY. Edited by MORRIS POLLARD, University of Texas Medical Branch, Galveston. Pp. 312; 49 ills and 2 color plates. New York: John Wiley & Sons, Inc., 1959. Price, $7.00.

THIS volume records the proceedings of a symposium held in memory of the late Dr. F. R. Beaudette, formerly of Rutgers University. It presents the papers of 18 specialists in the field and the extemporaneous discussions of these papers by 45 leading virologists. Among the topics discussed were: Some Aspects of Animal Virus Multiplication; Genetic Interaction between Bacteriophage and Bacteria; Virus Transformation and Cancer; Implications of 70 Newly Recognized Viruses in Man; Asian Influenza: A Challenge to Epidemiology; and Viral Neoplasia, including the Stewart-Eddy tumor-inducing virus.

In addition, there is a personalized tribute to Dr. Beaudette written by Dr. S. A. Waksman, and an interesting epilogue on Tulipomania by Dr. R. J. Dubos.

Although of primary interest for virologists, workers in cancer and other areas will also find important information and concepts in this volume. C.Z.

ELEMENTARY STATISTICS WITH APPLICATIONS IN MEDICINE AND THE BIOLOGICAL SCIENCES. By FREDERICK E. CROXTON, PH.D., Professor of Statistics, Columbia University. Pp. 376; 101 ills. New York: Dover Publications, Inc., 1959. Price, $1.95.

THIS paperbound edition of a book published in 1953, formerly entitled, "Elementary Statistics with Applications in Medicine," makes available in inexpensive form a fine text on elementary statistics.

Assuming a minimum knowledge of mathematics, this book defines the basic terms, concepts and techniques of statistics. It discusses frequency distributions, correlation data and time series. Tabular and graphic presentation of material, measures of variation and central tendency, dispersion, skewness and kurtosis, the normal curve, arithmetic mean, median and mode, sampling, design of experiment, binomial and Poisson distribution, are adequately covered. An analysis of relevance and significance of statistical measures, including a chapter on the chi-square test, is presented in detail. A vocabulary of symbols used precedes each chapter.

Valuable to all who use statistics and statistical methods, this book has a special appeal for students in medicine and the biological sciences, clinicians, laboratory and research workers. Numerous examples and applications from various fields of investigation are incorporated into the text. Fourteen numerical appendices and an index complete this sturdy edition of an expert volume. F.R.

REMINISCENCES AND ADVENTURES IN CIRCULATION RESEARCH. By CARL J. WIGGERS, M.D., Professor Emeritus of Physiology, Western Reserve University, School of Medicine. Pp. 416; 82 ills. New York: Grune & Stratton, Inc., 1958. Price, $9.75.

THIS is a most unusual and valuable book. Its first 187 pages (Reminiscences) constitute an autobiographical sketch of a man who is known all over the world as one of the greatest of all physiologists and circulation researchers. It is a well written sketch and one that will be much enjoyed by a host of ex-students, associates and friends as well as by many others who were not fortunate enough to have had contact with him but have admired his genius from afar. There should be found in these pages a motivating force for young physicians who wish to hitch their wagons to a star, hoping to emulate the great. It is exciting indeed to read the story of a young man with a superior intellect who finds the search for truth in the laboratory more rewarding than the usual path into a lifetime of practice.

The second half of the book is the part which is particularly unusual. It deals with many of the problems in cardiovascular physiology and pathophysiology which the author and his many associates attacked so vigorously and so brilliantly during his long lifetime of research. Especially interesting is the fact that the complexities of the problem as originally dealt with are considered and the route or routes followed in achieving the solution clearly portrayed, together with a description of the apparatus developed en route. For the one who has followed cardiovascular literature through recent decades there will be much nostalgia in all this. For the young investigator, however, the following of Dr. Wigger's clear reasoning in the attack upon a perplexing problem will be an invaluable

educational experience. Every academic physician should read this fine book, and all who do so will find profit and enjoyment.

T.D.

LEUKEMIA. By WILLIAM DAMESHEK, M.D., Professor of Medicine, Tufts University School of Medicine and FREDERICK GUNZ, M.D., PH.D., Hematologist, Christchurch Hospital, Christchurch, New Zealand. Pp. 420; 142 ills. New York: Grune & Stratton, Inc., 1958. Price, $15.75.

THIS is a splendid treatise on the leukemias. The authors have drawn upon a wealth of personal experience and thoroughly reviewed the pertinent literature in order to produce this timely, up-to-date monograph on the subject. Every aspect of leukemia is discussed, including: history; prevalence; etiology; pathology; course and special pathology as related to symptomatology; clinical and special features; differential diagnosis; laboratory diagnosis; the relation of leukemia to myeloproliferative disorders; prognosis; and treatment. In addition, the authors discuss what one should tell the patient with leukemia, and also leukemia in the future.

The text is profusely and beautifully illustrated. It is recommended to hematologists and others who are concerned with this serious group of disorders. C.Z.

CONNECTIVE TISSUE, THROMBOSIS AND ATHEROSCLEROSIS. Proceedings of a Conference held at Princeton, May 12-14, 1958. Edited by IRVINE H. PAGE, M.D., Cleveland Clinic Foundation. Pp. 316; 118 ills. New York & London: Academic Press, Inc., 1959. Price, $9.50.

THERE has been so much emphasis upon derangements of lipid metabolism in the genesis of atherosclerosis in recent years that the other facets of this complex problem are often forgotten or underemphasized. In organizing the conference the transactions of which are recorded in this book, Dr. Page brought together a group of investigators in the connective tissue field and another group who have dealt with the problem of fibrinolysis. The intent was to let those who are not primarily "atherosclerotic" have their say. The result has been a very stimulating and provocative volume. The very active discussion following each paper has been recorded *in toto* and this includes some of the best reading in the book. Excellent reproduction of illustrations contributes much to the success of the effort. Fortunately, there is a complete subject and author index to facilitate its use. The book can be read with great profit by internists, pathologists and cardiovascular disease investigators. T.D.

PHYSIOLOGY OF CARDIAC SURGERY. By FRANK GOLLAN, M.D., Assistant Director of Professional Services for Research, Veterans Administration Hospital; Research Associate, Department of Surgery, Vanderbilt University Medical School, Nashville, Tenn. Pp. 96; 18 ills. Springfield, Ill.: Charles C Thomas, 1959. Price, $4.50.

AN unbiased appraisal of hypothermia and extracorporeal circulation, written in a delightful style, with the refreshing absence of some author's pet invention; a rarity in today's literature of this field.

There is no subject more difficult for an author than one which is constantly changing, where the truths of today are the falsehoods of tomorrow. Dr. Gollan's essay on recent advances in cardiac surgery places some of the controversial issues of this field in their proper perspective. It is certainly a thought-provoking essay and should be well recommended for the library of any cardiac research laboratory. W.W.

TEXTBOOK OF PEDIATRICS. Edited by WALDO E. NELSON, M.D., B.Sc., Professor of Pediatrics, Temple University School of Medicine; Medical Director of Saint Christopher's Hospital for Children. 7th ed. Pp. 1463; 427 ills. Philadelphia: W. B. Saunders Co., 1959. Price, $16.50.

THE 7th edition of this text has been brought completely up-to-date by the editor with the collaboration of many of the authors of the preceding edition and seventeen new contributors. Every chapter has been revised and new chapters and sections have been added, thereby making the text representative of current pediatric thought and practice. Among rewritten subjects are clinical appraisal of infants and children, parenteral fluid therapy, anesthesia, the newborn infant, tuberculosis, respiratory physiology and its application to pulmonary disease, the nervous system.

Because of these advances and because of experienced editing, much of the material has been reclassified, resulting in a logical text with more continuity of thought.

Every page of the 7th edition has been

reappraised in an effort to delete repetitious or obsolete paragraphs, sentences or words, and when indicated, to substitute more pertinent ones. The result is that the language of this comprehensive pediatric textbook is excellent, its style is lucid and it is shorter than the previous edition by 119 pages.

Students and physicians seeking for a better understanding of the medical problems of infants and children in their homes and communities will welcome this book.

E.B.

HYPERTENSIVE DISEASE: DIAGNOSIS AND TREATMENT. By SIBLEY W. HOOBLER, M.D., University of Michigan Medical School and University of Michigan Hospital. Pp. 353; 16 ills. New York: Paul B. Hoeber, Inc., 1959. Price, $7.50.

THIS is an up-to-date book upon the study and treatment of patients with hypertensive disease. It is divided into five sections; the first, secondary hypertension susceptible to cure; the next, secondary hypertension not susceptible to cure; the third, primary hypertension; the fourth, principles underlying the treatment of primary hypertension and its complications; and the final one, use of specific treatment regimens to reduce blood pressure. In addition, there is a section of 60 pages containing 12 appendices which contain techniques for tests and treatment of hypertension some of which are useful for quick reference.

The various therapeutic agents in the management of hypertensive states are adequately discussed, and the numerous case histories illustrate the technique of use of these agents especially when combined therapy is employed.

This book should be helpful to the clinician who deals with problems of hypertension.

I.G.

DERMATOLOGIE UND VENEREOLOGIE BAND III, TEIL I. Edited by H. A. GOTTRON UND W. SCHÖNFELD. Pp. 695; 232 ills. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $39.30.

STATEMENTS about volume II, parts 1 and 2, of this projected five-volume work, were published in this Journal in April and May, 1959, respectively. Volume III, part 1, is worthy of its predecessors both from the standpoint of continued excellence physically and in content. This volume contains material dealing with cutaneous changes produced by external factors, in which are included: thermal and electrical injuries to the skin, cauterizations following damage to the skin by war materials; foreign body deposits; artefacts; light dermatoses; disturbances of peripheral blood flow, as a result of the varicose symptom complex; varicose veins and varicose symptom complex; the anal symptom complex; allergic diseases and toxic injuries to the skin; and various aspects of eczema. The material on these subjects is fully documented by pertinent literature references but the author and subject indices will appear in volume III, part 2.

H.B.

LIPIDOSES: DISEASES OF THE INTRACELLULAR LIPID METABOLISM. By SIEGFRIED J. THANNHAUSER, M.D., PH.D., HON.M.D., Universities of Freiburg, Munich, Dusseldorf, Clinical Professor of Medicine Emeritus, Tufts College Medical School. 3rd ed. Pp. 600; 126 ills. New York: Grune & Stratton, Inc., 1958. Price, $19.75.

IN view of the many significant advances in the laboratory and clinical aspects of lipids during recent years, a revised edition of this highly regarded book is particularly welcome at this time. The author has retained essentially the same clinical classifications and framework as before, with the following major sections: 1) The Physiology and Chemistry of Lipid Metabolism; 2) Hyperlipemia; 3) Xanthomatoses; 4) Gaucher's Disease (Reticular and Histiocytic Cerebrosidosis); and 5) Niemann-Pick's Disease (Reticular and Histiocytic Sphyngomyelinosis).

The literature has been carefully reviewed, and the material has been revised and supplemented extensively. As before, there are numerous illustrations which enhance an already excellent text. This book is recommended to all who are interested in the broad spectrum of lipidoses.

C.Z.

PATHOLOGIC PHYSIOLOGY OF ORAL DISEASE. By RICHARD W. TIECKE, B.S., M.S., F.A.C.D., Professor of Pathology, Northwestern University Dental School; ORION H. STUTEVILLE, B.S., D.D.S., M.D., Professor and Chairman, Department of Maxillofacial Surgery and Chairman, Department of Oral Surgery, Northwestern University Dental School, and JOSEPH C. CALANDRA, M.D., PH.D., Professor and Chairman, Department of Pathology, Medicine and Bacteriology, Northwestern University Dental

School. Pp. 480; 637 ills. St. Louis: C. V. Mosby Co., 1959. Price, $11.50.

This volume fills a previously existing gap in the literature dealing with pathologic processes in oral structures. Its most important innovation is a comprehensive correlation of the clinical aspects with the microscopic pathology. Since competent texts have been written on dental caries, anomalies of the teeth, pulp pathology, and pathology of peridontal disease, these subjects are treated briefly but supplemented with carefully selected references. On the other hand, the specific inflammatory oral diseases and the lesions caused by viruses, allergy, drug therapy, metabolic and deficiency abnormalities and blood dyscrasias are discussed in commendable detail. The chapters on normal structures commonly mistaken for oral abnormalities, hypertrophy, hyperplasia and repair overgrowth are outstanding contributions to the field. Most appropriately, coverage is given to benign tumors of the head and neck as well as to those of the oral cavity. Much valuable new material is presented on dental granuloma, odontogenic cysts and tumors, and traumatic bone space. The text is profusely illustrated and the bibliography appended to each chapter has been selected with unusual discrimination. This book is highly recommended to practitioners of medicine and dentistry. H.S.

Cholesterol. By David Kritchevsky, Associate Member, The Wistar Institute, University of Pennsylvania. Pp. 291. New York: John Wiley & Sons, Inc., 1958. Price, $9.75.

The author has brought together in this book a large volume of pertinent material on the biologic function and significance of cholesterol. Discussed in turn are the chemistry, biosynthesis, absorption and transport, and metabolism of cholesterol. Then the role of cholesterol in disease states is considered, followed by chapters on the blood cholesterol and the analysis of cholesterol.

The presentation is thorough, readable, and concise. The book is recommended to anyone interested in obtaining an objective review of the current status of cholesterol in human metabolism and disease. C.Z.

The Reticulo-Endothelial System in Growth and Tumor Formation. By Roger Wyburn-Mason, M.A., M.D.(Cantab.), M.R.C.P.(London), Late Clinical Research Fellow, Royal Marsden (Cancer) Hospital. Pp. 206; 79 ills. London: Henry Kimpton, 1958 (Rittenhouse Book Store, Philadelphia, U.S. Agents). Price, $8.00.

This is a timely monograph on the reticulo-endothelial system, written by one well-qualified for the task through much study and experimentation. The material is presented in three major sections: Part I. Introduction and Experimental Observations. Here the reticulo-endothelial cells and the histiocytic system are described, followed by discussions of experimental techniques, and of vital staining and distribution of cells of this system in normal as well as malignant tissues. In Part II. The Role of Macrophages in Normal Tissue, the control of feeding and excretion of other body cells by cells of the R-E system is considered. Also discussed is the nervous control of R-E cell activity, and the influence of macrophages and nervous impulses on tissue regeneration and embryonic development. Part III is entitled, The Role of Macrophages in Tumors. Among the topics discussed in this section are the agents known to be concerned in tumor formation, somatic mutation, congenital anomalies, and the mutant-like nature of malignant cells.

The text is beautifully and painstakingly illustrated. The results justify the long periods of waiting at operations which the author found necessary in order to obtain human material suitable for his special preparations.

The R-E system has long been considered to have important protective functions. As may be gathered from the foregoing titles, it also appears to play dynamic roles in other areas not well appreciated heretofore. This book is recommended to all who wish to gain better insight into the scope and functions of the reticulo-endothelial system.

C.Z.

The Strategy of Chemotherapy. Edited by S. T. Cowan and Elizabeth Rowatt. Pp. 360; 43 ills. New York: Cambridge University Press, 1958. Price, $7.00.

This volume contains the papers presented at the Eighth Symposium of the Society for General Microbiology, held in London, April, 1958. As is characteristic of all the symposia in this series, the articles are competently written by individuals who are recognized authorities in the fields discussed. Among the topics considered at this meeting are: The Relation of Strategy to Tactics: Some General Biochemical Principles; The Antibi-

otic Approach; Surface-Active Bacteriocides; Metal-binding Agents in Chemotherapy; the Activation of Metals by Chelation; The Designing of Antimetabolites; Mechanisms of Chemotherapeutic Synergy; The Chemotherapy of Bacterial Infections; The Chemotherapy of Fungal Diseases; and The Chemotherapy of Some Protozoal Infections.

The presentations are basically oriented and carefully survey the present position in the areas dealt with. Microbiologists, pharmacologists, biochemists, and internists and pediatricians who are particularly concerned with infectious diseases will find this a valuable and stimulating group of articles.

C.Z.

PANCREATITIS. By HERMAN T. BLUMENTHAL, PH.D., M.D. AND J. G. PROBSTEIN, M.D., Director, Institute of Experimental Pathology, The Jewish Hospital and Associate Professor of Pathology, St. Louis University, School of Medicine, St. Louis, Missouri; and Director Emeritus, Division of Surgery, The Jewish Hospital, Associate Professor of Clinical Surgery, Washington University, School of Medicine and Assistant Professor of Anatomy, Washington University, School of Dentistry, St. Louis, Missouri, respectively. Pp. 379; 58 ills. Springfield, Ill.: Charles C Thomas, 1959. Price, $9.50.

THIS is a complete and authoritative text on acute pancreatitis, representing the experience of the authors based on 163 necropsy cases. From this series of cases they have presented the clinical-pathological correlation of acute pancreatitis and have covered the subject matter in a comprehensive, clear and concise manner. Perhaps one would have appreciated a more thorough discussion of chronic pancreatitis, since the etiology and background of this pathological process is somewhat obscure, but actually the authors set out to limit their remarks primarily to the acute form of the disease in its varying degrees of severity.

A.P.

THEORIE DES ORGANISMUS. By PROF. MED. K. E. ROTHSCHUH, Physiologic Institute of the University Münster i. W., Pp. 330; 33 ills. München and Berlin: Verlag Von Urban and Schwarzenberg, 1959. Price, DM 48.

THIS outstanding book presents an attempt to comprehend the nature of man scientifically without the help of philosophy or theology. The "theory of the organism" which is developed here comprises life (bios), soul (psyche) and disease (pathos).—*Life* can be understood only if in addition to the causes and effects of the processes of life their "bionome" significance in relation to the organism as a whole is taken into consideration. This "bionome organization" is emphasized throughout the book. Some of its principles are ontogenesis, species-specific functions, propagation and self preservation. The *soul* is a phenomenon of life. Its processes are divided into biopsyche (drives), thymopsyche (emotions), eidopsyche (perception) and noopsyche (thinking). These undergo both ontogenesis and phylogenesis. Animals, too, have souls, but thinking occurs only in higher animals (dogs, monkeys). Man differs from animals by the enormous capability of his central nervous system to remember experiences, to connect them properly, and to use them for the solution of new problems. Through this capability an individual can acquire in short time the experiences of many centuries. This shows the extraordinary importance of education for the progress of the human race. The author continues that it is a fact that all psychological reactions depend on activities of the central nervous system. They can be suppressed by leukotomy or other organic interventions. The soul can therefore not be a cofactor of neurophysiological activity (reciprocal effect theory) nor can it be the director of this activity (pianoplayer theory), but as indicated already by Hering, Bleuler and others, it appears to be nothing but the inner perception of somatic-neurophysiological processes. This is not a materialistic theory. On the contrary, according to this hypothesis, the soul is as real as the soma. However, the soul does not lead the brain. On the contrary, the brain leads the soul. In other words, the soul is no *causa efficiens*, but it is a *qualitas accidens*. The author then explains that the soul is related to the bionome organization through its principles which though governing primarily the biosomatic sphere are perceived psychologically as dull pressure or drives. The latter include the drive to improve one's personality, to propagate and to preserve oneself. The drive to propagate, the sex drive, was unduely emphasized by Freud. From these various observations the author concludes that the belief that the psyche can influence the soma is an illusion of judgment. Life and soul cannot be understood without knowing *disease*. Somato- and psychopathology are as integrated as normal bios and psyche. Psychological non-neurotic disturbances and neuroses arise most likely through activation of the vegetative nervous or endo-

crine system. This activation is not due to the action of psyche. It is preceded by the influx of stimuli from the sensory systems. The psychological experience in these cases is merely an associated phenomenon.

This clear, thoughful and comprehensive discussion of the burning problem of soma and psyche is highly recommended to all students of psychology, psychosomatic medicine and psychiatry who read German well. Its translation into English seems highly desirable. W.E.

Modern Trends in Pathology. Edited by Douglas H. Collins, O.B.E., M.D., F.R.C.P. and written by sixteen collaborators. The Editor is Professor of Pathology, University of Sheffield; the contributors are experts in their fields and the majority are of professorial rank. Pp. 334; 135 ills. New York: Paul B. Hoeber, Inc., 1959. Price, $15.00.

This is an interesting and stimulating book. It covers a wide range of subjects including such topics as the injured cell, the localization of antibody production, cancer of the liver and disorders arising from the human trophoblast, to name a few. The contributors are experts in their field and each chapter is written in a concise, clear and authoritative fashion. The editor is to be congratulated for his choice of articles and for his collaborators. This is truly a book not only to be enjoyed, but to serve as a source of knowledge and of reference. A.P.

An Atlas of Normal Radiographic Anatomy. By Isadore Meschan, M.A., M.D. Bowman Gray School of Medicine of Wake Forest College. 2nd ed. Pp. 759; 1446 ills. Philadelphia and London: W. B. Saunders Company, 1959. Price, $16.00.

Since the first edition of Normal Radiographic Anatomy was published in 1951, the Atlas has established itself as a workable reference especially for radiology residents. The second edition follows much the same format but there have been some changes and additions. As previously, the text emphasizes basic morbid anatomy as applied to radiography. Among the major changes are the modifications and additions to the chapters on the radiographic study of the brain and cardiovascular system. The chapter on bone growth and development has been rewritten. A chapter on radiation protection has been added.

The tracings are as before, excellent, and there have been additional reproductions.

The purpose of this edition, namely to present a practical useful text for medical students, general practitioners, residents, especially in Radiology, and Roentgen-ray technicians, has been accomplished. H.W.

Advances in Psychiatry. Edited by Mabel Blake Cohen, M.D. Private Practice of Psychoanalysis. Pp. 314. New York: W. W. Norton and Co., Inc., 1959. Price, $4.95.

Advances in Psychiatry represents a collection of some of the outstanding articles which have appeared in the journal, Psychiatry, in the last 20 years. The journal Psychiatry has always selected as its field of particular interest that zone where psychological, biological, and social sciences come together.

The contents of the book consist of an introduction by Dr. Mabel B. Cohen. There are sections on Values and Philosophy; Psychiatry and Culture; Schizophrenia; and Clinical and Therapeutic.

The purpose of the book is to expand the theories of personality development by taking into account the contributions of psychoanalysis; the contributions of more recent work in the interactional aspects of behavior; and integrate these contributions with the more recent understanding of the structure and physiology of the nervous system.

In this book one finds an interesting collection of papers that many psychiatrists may have already read. M.B.

Trauma. By Harrison L. McLaughlin M.D., College of Physicians and Surgeons, Columbia University. Pp. 784; 407 ills. Philadelphia: W. B. Saunders Company, 1959. Price, $18.00.

Twenty authors have contributed to this book. All but one of the authors are or have been members of the attending staff of the Columbia-Presbyterian Medical Center and of the College of Physicians and Surgeons of Columbia University. The volume consists of twenty-five chapters divided into five parts. Part I includes chapters devoted to the response to injury, general principles in the treatment of trauma, infection and antibacterial agents in trauma, vascular injuries and thermal trauma. Part II has five chapters presenting injuries to the upper extremity. Part III, five chapters, discusses lower extremity injuries. Injuries to the trunk, including the chest and abdomen, are covered in

six chapters in Part IV. The last part devotes four chapters to injuries involving the head and special senses.

The subject matter is well organized. Most chapters devoted to a specific region have an introductory section that outlines the pertinent surgical anatomy of the region. Basic principles of management are emphasized and re-emphasized. Multiple injuries and priority of treatment are thoroughly discussed in more than one section. The illustrations are adequate, clear, simple and not cluttered by unnecessary details.

As noted in the Preface, "the preparation of a monograph on Trauma is not an easy task . . ." and "consequently, much potentially pertinent material must be omitted . . ." Some readers with special interests will find points for disagreement with the authors, particularly in the "open" vs. "closed" management of fractures. Other readers will consider some areas, such as urologic injuries, fluid and electrolyte balance, anesthesia for the injured, plastic surgery, inadequately covered. In general, however, the authors are to be complimented on the net result. The book will be useful for students, residents, and general physicians who are called upon to manage the injured. V.L.

L'Auto-immunisation en Pathologie. By Simone Stadtsbaeder, Universite Catholique de Louvain, Laboratoires de Bacteriologie. Pp. 185; 20 ills. Brussels: Editions Arscia, 1959.

This volume presents an attempt at analysis of the role of autoimmunization in the pathogenesis of glomerulonephritis, encephalomyelitis, and certain acquired hemolytic syndromes. The author claims to have produced glomerulonephritis in rabbits by injection of versenized monkey-kidney-cell cultures in the absence of anti-rabbit-kidney antibody, but no clinical data are given, and the illustrations do not support his claim. His conclusion that autoimmunization is not involved in glomerulonephritis is therefore without base of fact. Encephalomyelitis was produced in guinea pigs by injection of homologous brain emulsion in Freund's adjuvant. As no antibody against red cells sensitized with aqueous brain extract could be demonstrated, the author thinks that a toxic rather than immunological mechanism should be considered. However, he admits that the tuberculin-type of allergy could not be ruled out. His experiments with hemolysis were similarly undecisive. After discussing cytotoxic effects of antibodies, auto-antigenicity and various immunotoxic mechanisms, the author concludes that the role of auto-immunization in disease has not been completely proved. W.E.

Diseases of the Nose, Throat and Ear. Edited by Chevalier Jackson, M.D., and Chevalier L. Jackson, M.D. 2nd ed. Pp. 886; 1193 ills. Philadelphia: W. B. Saunders Co., 1959. Price, $20.00.

This excellent text in its second edition conforms to the general format of the original edition published in 1945 which was well received by students of the subject as well as qualified specialists.

Although this book is edited by the late Dr. Chevalier Jackson and his son Dr. Chevalier L. Jackson, both eminent laryngologists and bronchoesophagologists, the text in diseases of the nose, pharynx and ear are very competently written by sixty-one outstanding authorities on these subjects.

The changes from the first edition are principally in the up-to-date material presented by the new contributors who have replaced those who are inactive or deceased.

This volume has many outstanding features. I was particularly impressed with the new sections of "Hematologic Aspects of Otonasopharyngeal Disorders" by Dr. Tocantins, "The Deaf Child" by Dr. David Myers and the "Examination of the Ear and Hearing Tests" by Dr. Fred Harbert.

The illustrations are excellent throughout the book. As in the first edition the color plates of laryngeal and esophageal diseases are outstanding.

At the end of each author's contribution is an up-to-date bibliography on the subject which adds greatly to the reference value of the book. L.S.

Cutaneous Manifestations of the Malignant Lymphomas. By Samuel M. Bluefarb, B.S., M.D., Northwestern University Medical School. Pp. 534; 47 ills. Springfield, Ill.: Charles C Thomas, 1959. Price, $15.50.

Any physician, internist or surgeon, who has occasion to treat patients with lymphomas should have Bluefarb's book, one of the series of monographs on the cutaneous manifestations of the reticulo-endothelial system. Frequently, the cutaneous manifestations of these diseases are the first indication that a malignant lymphoma is present. Since the manifestations are so variable and at times

so similar for the different lymphomas, it is fortunate that we now have a documented, lucid, detailed and well illustrated account of the cutaneous lesions of mycosis fungoides, Hodgkin's disease and lymphosarcoma. In addition there is included a discussion of the immunological status of the malignant lymphomas. There is but little one can criticize in this presentation, but the author's view that mutation between the various malignant lymphomas does not occur will not be universally accepted. H.B.

ENTWICKLUNGSGESCHICHTE UND FEHLBILDUNGEN DER WIRLBELSÄULE. By PROF. DR. MED. GIAN TÖNDURY, Professor of Anatomy, University of Zürich. Pp. 196; 173 ills. Stuttgart: Hippokrates Verlag, 1959.

THIS monograph (volume 7 of a series devoted to problems of the spine) deals with the detailed embryology and intrauterine differentiation of the human spine and its various regions. It contains a wealth of largely new information based to a considerable extent on the author's own research. The developmental dynamics of the normal and abnormal spine are discussed on the basis of experimental embryology and genetics. The morphogenesis of the different types of malformations spontaneously occurring in the human spine are integrated with the experimental and animal observations. The book is clearly written by an expert in the field and the excellent and ample illustrations enhance the value serving as a documentary atlas of data not available elsewhere. The book is of great interest to all concerned with the structure and function of the spine. W.P.

DAS RÖNTGENSCHICHTBILD DES OHRES: THE TOMOGRAM OF THE EAR. By PROF. DR. KARL MÜNDNICH, Chief of Service, Clinic and Hospital for Diseases of the Throat, Nose and Ear, University of Munich, and DR. KURT-WALTER FREY, Technical Assistant, Institutes and Hospital for Physical Therapy and Roentgenology, University of Munich. Pp. 126; 205 ills. Stuttgart: Georg Thieme Verlag, 1959. Price, DM 66 ($15.75).

THIS is the most comprehensive treatise on sectional radiography of the ear to be published up to this time and contains explicit information concerning radiation dosage and protection, projections to be employed and the findings in diseases and malformations of the ear. The superb reproductions of radiograms, accompanied by excellent explanatory diagrams, are based on living subjects, but the authors have utilized new and extensive knowledge gained from examinations of the dry skull, postmortem dissection, and macerated temporal bones. Adjacent columns present the brief but adequate text in German and in English. A complete bibliography is included. This monograph is indispensable for all otolaryngologists and radiologists. H.S.

RADIODIAGNOSTIC EN OTOLOGIE. By MICHEL PORTMANN, M.D., Assistant Professor, Faculty of Medicine, University of Bordeaux, AND GEORGES GUILLEN, M.D., Chief of Clinic, Faculty of Medicine, University of Bordeaux. Pp. 210; 146 ills. Paris: Masson et Cie, 1959. Price, 3.700 fr.

THIS concise monograph on radiographic diagnosis of diseases and abnormalities of the ear contains much new information based on the experiences and original investigations of the authors. The opening chapter discusses the radiographic anatomy of the various structures of the ear and temporal bone and includes numerous instructive photographic reproductions and diagrams.

After first pointing out the deficiencies of general radiologic techniques, the second chapter enumerates and describes the refinements essential for satisfactory otologic examination and proceeds with individual assessments of the advantages and limitations of tomography and the procedures of Schuller, Chausse, Guillen, Stenvers, Mayer and Hirtz. The final section deals with the techniques of radiographic diagnosis of otologic abnormalities and embraces every important entity including glomus jugulare tumors, cancer, dystrophies of the otic capsule and anomalies of the Eustachian tube.

Although primarily written for otologists, the radiologist will find this treatise both informative and stimulating. H.S.

ORTHOPEDICS. By LEWIS COZEN, M.D., Attending Orthopedic Surgeon, Cedars of Lebanon Hospital, Los Angeles. 3rd ed. Pp. 430; 321 ills. Philadelphia: Lea & Febiger, 1959. Price, $9.50.

IT has long been my feeling that orthopedics, as taught in medical schools, has more or less been a form of preparation for students to become orthopedic specialists rather than general practitioners. With this thought, it becomes apparent that I heartily approve o

this text for students and general practitioners, for a knowledge of its contents would eliminate many visits to orthopedic specialists, something the patient at least would appreciate. However, let me add that it behooves the specialist to keep abreast of current office procedure, which this text will help him do.

The section on plaster of Paris casts and splints is a concise, lucid description which many a pure orthopedist would do well to review. Chronic foot problems as corns, calluses. Morton toe and the like are presented well. In fact the many subjects discussed are all well presented. In conclusion, I feel strongly about this text and would urge its use in medical school, interneship and certainly in general practice. A.S.

GRAY'S ANATOMY OF THE HUMAN BODY. Edited by CHARLES MAYO GOSS, M.D. 27th ed. Pp. 1458; 1174 ills. Philadelphia: Lea & Febiger, 1959. Price, $17.50.

THE new, 100th anniversary edition of this classic textbook on anatomy surpasses in practical informative value for students and practitioners of medicine and surgery any previous edition, of which there have been 26 with a total sale of 572,500 copies.

Problems facing the editor in the new edition were amplification, simplification and elimination. This arduous and judicious task was efficiently accomplished as attested by the following: The central nervous system was completely rewritten and reduced in length by 50 pages. Embryology and histology of the nervous system are well summarized. The sympathetic nervous system is more effectively illustrated by the addition of Töndury's regional body sections. The heart chapter was completely rewritten. The addition of 11 heart figures of Rauber-Kopsch with printed labels on the structures shown in the drawing are time saving and extremely helpful, as characteristically in Gray's text, always have been the similarly labeled drawings in the osteology chapter, which, to date, has seldom been matched in detailed captioning, artistic and scientific precision.

Arteries and veins along with their embryology are discussed in separate chapters. The arteries of the upper abdominal organs are described and illustrated more fully than before, thereby affording a much safer approach to surgical procedures in this region. The endocrine system was rewritten, but is a bit short. In view of present surgical resections of the liver and kidney, one misses a description of the segmentation of these organs along with the intraorganic distribution of their blood vessels. The vertebral vein system, while discussed in a paragraph, should have been more fully appraised and illustrated. A noteworthy, highly valuable item, is the retention of the chapter on surface and topographical anatomy. While the new Paris nomenclature is fully adopted, many proper name references in common use by surgeons (for example, Poupart's lig.) are meritoriously retained. The bibliographic references listed after each chapter are very numerous and excellently chosen as regards their comprehension and merit. Despite the many new additions made, the essential character of Gray's Anatomy is retained. N.M.

HANDBOOK OF TOXICOLOGY, VOLUME III: INSECTICIDES. By WILLIAM O. NEGHERBON, Loyola College, Baltimore. Prepared under the direction of the Committee on The Handbook of Biological Data, Division of Biology and Agriculture, The National Academy of Sciences, The National Research Council. Pp. 854. Philadelphia: W. B. Saunders Company, 1959. Price, $14.00.

THIS third volume of the Handbook of Toxicology is an extensive compendium on the toxicology of insecticides. As such it should prove to be an extremely valuable reference for all those concerned with the problem of toxicology. The book is arranged in 188 sections, of which 164 concern individual agents and 24 deal with general topics. The contents are alphabetically arranged. The section devoted to a particular agent contains everything pertinent to that particular agent without the necessity of cross reference to other parts of the book. The resulting repetition of comparative information about a given group of compounds is more than made up for by convenience in using the book. The book contains an index of scientific and common names of insects, other animals, and plants mentioned in the text. There is also an extensive index of chemical compounds with all available designations alphabetically arranged and with appropriate cross references. The book is documented by a bibliography containing 3404 references. R.S.

TIME DISTORTION IN HYPNOSIS. By LINN F. COOPER, M.D., Associate Professor of Clinical Medicine, Georgetown University Medical Center, and MILTON H. ERICKSON, M.D.,

Formerly Associate Professor of Psychiatry, Wayne University College of Medicine. 2nd ed. Pp. 206; 8 ills. Baltimore: The Williams & Wilkins Co., 1959. Price, $4.00.

IN this book, the authors describe the concept of subject hypnotic time distortion. Clocks do not truly measure, or compare quantities of experiential time. There can be a wide variance between the actual clock time and the seeming duration of the time during which some event occurred. This same time distortion event can be deliberately induced under hypnosis.

Time distortion in hypnosis according to the authors is important not only in the field of experimentation, but it can be applied to the field of clinical and therapeutic problems.

This book will appeal to persons interested in the subject of hypnosis and it is a contribution to the subject of temporal perception. This reviewer would question the value of this book to the psychotherapist. M.B.

GRUNDRISS DER PHYSIOLOGISCHEN CHEMIE FÜR VETERINARMEDIZINER, HUMANMEDIZINER UND BIOLOGEN. BY MARTIN SCHENCK AND ERICK KOLB, both of the Karl-Marx University of Leipzig. 3rd ed. Pp. 333; 18 ills. Jena: Gustav Fischer Verlag, 1959. Price, DM 23.80 (about $10.00).

IF this is a representative example of East German (and by implication, Russian) textbooks, a considerable emphasis on their importance must be considered as demonstrated. As a basic textbook in the field of Physiological Chemistry, it leaves little to be desired, and it is very much up-to-date with recent advances in knowledge without indicating the controversies which do little but confuse the beginning student.

There is a limited but very well integrated inclusion of short sections on physiological actions of the various compounds, for example, steroids, vitamins, hormones, as they are covered in the discussion. There are some areas not well covered. For example, the description of the activation of plasma thromboplastin is almost completely ignored and no mention of specific coagulation defects is made.

A translation in English would be very acceptable as a text for first year medical students. J.B.

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DR. RICHARD A. KERN, Temple University Hospital, Philadelphia 40, Pa.

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